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Expanded Newborn Screening in Texas: A Cost-effectiveness Analysis Using Markov Modeling

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Expanded Newborn Screening in Texas: A Cost-effectiveness Analysis Using Markov Modeling

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May, 2009

Dedication

To my parents for teaching me the value of education

To Amol for having faith in my abilities and for walking with me every step of the way

Acknowledgements

I do not have enough words to express my gratitude to Dr. Karen Rascati, my dissertation supervisor, for her constant guidance and support throughout the dissertation project. Her faith in my ability to produce good quality work helped me overcome fear and discouragement on numerous occasions. It is only because of her tireless nurturing and encouragement that I was able to move forward with my research ideas.

I am grateful to my committee members: Dr. David Warner, Dr. James Wilson, Dr. Kenneth Lawson and Dr. Jamie Barner for their valuable inputs on this project. Their knowledge and expertise were instrumental in giving shape to my research ideas.

I am thankful to Dr. Margaret Drummond Borg, Dr. Larry Sweetman and Dr. Scott Grosse for their expertise in their respective research areas. Their timely inputs helped me progress with this project. I am also thankful to my colleagues at the Texas Department of State Health Services who provided data and expert opinion.

I am especially thankful to the faculty members of the division of Pharmacy Administration for building a strong foundation that is necessary for succeeding in my future research endeavors.

Fellow graduate students also deserve special thanks for being a source of encouragement and inspiration. I would like to thank Ms. Mickie Sheppard for providing guidance and for her prompt resolution of matters related to course registration and financial aid. I am also grateful to Ms. Iris Jennings for her administrative support.

I would like to thank my parents who were always there for me whenever I needed help. They traveled overseas many times just so that I could focus on my graduate work while they helped with house work and childcare. Their lessons in

courage and hard work taught early in life helped me overcome many of my personal shortcomings and realize my potential in academics and in life.

Last, but not the least, my dear husband Amol and my beloved children Zubair and Sukham were a huge motivating factor. My graduate work at the University of Texas would not have been possible without their unconditional love and support. Thank you!

Expanded Newborn Screening in Texas: A Cost-effectiveness Analysis Using Markov Modeling

Publication No._____

Simrandeep Kaur Tiwana, Ph.D.

The University of Texas at Austin, 2009

Supervisor: Karen L. Rascati

Texas House Bill 790 resulted in the expansion of the newborn screening panel from 7 to 27 disorders. The long-term economic implications of this expansion have not been studied. The objective of this study was to estimate the incremental cost-effectiveness of the expanded newborn screening program compared to the previous standard screening in Texas.

A Markov model (for a hypothetical cohort of Texas births in 2007) was constructed to compare life-time costs and QALYs between the expanded newborn screening and pre-expansion newborn screening. Estimates of costs, probabilities of sequelae, and utilities for disorder categories were obtained from Texas statistics, the literature, and expert opinion. A baseline discount rate of 3% was used for both costs and QALYs, with a range of 0% to 5%. Analyses were conducted from a payer's perspective, so only direct medical cost estimates were included.

The life-time incremental cost-effectiveness ratio (ICER) for expanded versus pre-expansion screening was about $12,000/QALY. Probabilistic sensitivity analysis

using key variables showed that results ranged from about $9,500 to $13,000 /QALY. This range is well below the commonly cited willingness to pay threshold of $50,000/QALY.

Therefore, expanded newborn screening results in additional expense to the payer but also improves patient outcomes by preventing avoidable morbidity and mortality. The screened population benefits from greater QALYs as compared to the unscreened population. Overall, expanded newborn screening in Texas was estimated to be a cost-effective option as compared to unexpanded newborn screening.

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List of Abbreviations Used

1. ACMG: American College of Medical Genetics
2. ARC: Association of Retarded Children
3. ASA: Arginosuccinic Acidemia
4. CAD/C$: Canadian Dollar
5. CAH: Congenital Adrenal Hyperplasia
6. CBA: Cost-Benefit Analysis
7. CDC: Centers for Disease Control and Prevention
8. CEA: Cost-Effectiveness Analysis
9. CF: Cystic Fibrosis
10. CIT: Citrullinemia
11. CH: Congenital Hypothyroidism
12. COAD: Classical Organic Acid Disorders
13. CORN: Council of Regional Network for Genetic Services
14. CUA: Cost-Utility Analysis
15. DSHS: Department of State Health Services
16. ER: Emergency Room
17. GA I: Glutaric Acidemia Type I
18. GBP: Great Britain Pound
19. HMO: Health Maintenance Organization
20. HCY: Homocystinuria
21. ICER: Incremental Cost-effectiveness Ratio
22. IEM: Inborn Error of Metabolism
23. IOM: Institute of Medicine

24. IVA: Isovaleric Acidemia
25. MCADD: Medium Chain Acyl-CoA Dehydrogenase Disorder
26. MCHB: Maternal and Child Health Bureau
27. MMA: Methylmalonic Acidemia
28. MS/MS: Tandem Mass Spectrometry
29. MSUD: Maple Syrup Urine Disease
30. NAS: National Academy of Sciences
31. NTBC: 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione
32. NNSGRC: National Newborn Screening and Genetic Resource Center
33. OTA: Office of Technology Assessment
34. PA: Propionic Acidemia
35. PKU: Phenylketonuria
36. QALY: Quality Adjusted Life Year
37. Rc: Ceiling Cost Ratio
38. SIDS: Sudden Infant Death Syndrome
39. SCD: Sickle Cell Disease
40. TYR: Tyrosinemia
41. USD: United States Dollar
42. WTP: Willingness to Pay

Chapter One - Background

1.1 INTRODUCTION

Newborn screening is an integral part of public health interventions in the United States. It involves the screening of blood samples of newborn babies to detect genetic disorders of metabolism. Screening allows healthcare providers to diagnose potentially serious and life-threatening disorders. Ideally, screening should be conducted in the first week of a baby's life so that treatment can be initiated before the age of four weeks. Early diagnosis and treatment helps prevent irreversible mental retardation, physical disability and death in most cases.[1]

1.2 HISTORY

The twentieth century saw the discovery of many heritable disorders that were metabolic in origin and could therefore be detected via biochemical testing (collectively called newborn screening). Phenylketonuria (PKU), a disorder characterized by accumulation of unmetabolized phenylalanine in blood, was one of the first conditions to be described in this heterogeneous group of disorders. Therefore, the early history of newborn screening is synonymous with the history of PKU screening. [2]

1.2.1 Discovery of PKU

Phenylketonuria was first described in 1934 by Norwegian physician and biochemist Asbjörn Fölling. In his research on two mentally retarded siblings, Dr. Fölling demonstrated that the urine of PKU-affected children contains phenylpyruvic acid that results from elevated levels of phenylalanine in blood. These findings were later

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1 Therrell BL, Jr. U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab.* Sep-Oct 2001;74(1-2):64-74.

2 Paul D. *The history of newborn phenylketonuria screening in the US.* Bethedsa, MD: National Institute of Health; 1997.

supported with research in eight other children. Subsequently, Dr. Fölling also explained the genetic basis of the disorder.[3]

1.2.2 A Simple Test for Detecting PKU

In the early 1960s, Dr. Robert Guthrie, an American microbiologist, developed a simple and inexpensive bacterial inhibition assay for identifying infants with PKU. He also developed a technique of collecting blood samples on filter paper which made it possible for the first time to implement PKU screening at the population level.[4]

1.2.3 Policy Formulation

Dr. Guthrie's work coincided with a wave of new awareness and attitudinal change regarding mental retardation that had started in the 1950s. In 1950, Nobel laureate and Pulitzer prize-winning author Pearl Buck wrote an article about her PKU-stricken daughter Carol. Buck's article, originally published in the May 1950 issue of the *Ladies Home Journal*, later evolved into a book titled "The Child Who Never Grew." Hoping for a treatment for her daughter's illness, Buck concluded her book with the following words: "What has been, need not forever continue to be so. It is too late for some of our children, but if their plight can make people realize how unnecessary much of the tragedy is, their lives, thwarted as they are, will not have been meaningless."[5]

In 1961, this new technique for diagnosing PKU was tested on 400,000 infants from 21 states in a trial initiated by the Children's Bureau. In the same year, President John F. Kennedy, who had a mentally retarded sister named Rosemary, promised a two-fold increase in federal funding on retardation research. He also appointed a Presidential

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3 Folling A. [Phenylketonuria]. *Tidsskr Nor Laegeforen.* Mar 1 1967;87(5):Suppl:451-454.

4 Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics.* 1963;32:338-343.

5 Buck PS. *The Child Who Never Grew.* New York, NY: John Day & Co; 1950.

Advisory Commission on Mental Retardation. In 1962, this commission recommended mandatory PKU screening for every newborn. In 1963, the Children's Bureau began campaigning for screening with the slogan "Test Every Newborn for PKU."[6]

Meanwhile, the lay press was rife with articles that hailed the Guthrie test as a major breakthrough in preventing mental retardation. Lobbying for adoption of universal newborn screening gained momentum as advocacy groups like the National Association of Retarded Children and the March of Dimes became involved with the cause. With Massachusetts as the pioneer, many states had mandated screening by 1965 (Table 1.1).[7] This adoption was surrounded with skepticism. Opponents of mass PKU screening had concerns about the sensitivity and specificity of the test and believed that there was insufficient evidence that early detection of the disease could completely prevent mental retardation. They argued that as such, PKU is a rare disorder that accounts for less than one percent of all cases of mental retardation.[8]

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6 Paul D. *The history of newborn phenylketonuria screening in the US.* Bethedsa, MD: National Institute of Health; 1997.

7 Therrell BL, Adams J. Newborn screening in North America. *J Inherit Metab Dis.* Aug 2007;30(4):447-465.

8 Paul D. *The history of newborn phenylketonuria screening in the US.* Bethedsa, MD: National Institute of Health; 1997.

Table 1.1 Date Screening Mandated in US Newborn Screening Programs

Jurisdiction	Date of Statutory Provision of Newborn Screening	Jurisdiction	Date of Statutory Provision of Newborn Screening	Jurisdiction	Date of Statutory Provision of Newborn Screening
Alabama	1965	Kentucky	1966	North Dakota	1967
Alaska	1965	Louisiana	1964	Ohio	1965
Arizona	1979	Maine	1965	Oklahoma	1965
Arkansas	1967	Maryland	1965	Oregon	1963
California	1965	Massachusetts	1963	Pennsylvania	1965
Colorado	1965	Michigan	1965	Rhode Island	1965
Connecticut	1965	Minnesota	1965	South Carolina	1965
Delaware	1962	Mississippi	1985	South Dakota	1973
District of Columbia	1980	Missouri	1965	Tennessee	1968
Florida	1965	Montana	1965	Texas	1965
Georgia	1966	Nebraska	1967	Utah	1965
Hawaii	1965	Nevada	1967	Vermont	1962
Idaho	1965	New Hampshire	1965	Virginia	1966
Illinois	1965	New Jersey	1964	Washington	1967
Indiana	1965	New Mexico	1966	West Virginia	1965
Iowa	1965	New York	1964	Wisconsin	1965
Kansas	1965	North Carolina	1983	Wyoming	1983

Source: Therrell BL, Adams J. Newborn screening in North America. *J Inherit Metab Dis.* Aug 2007;30(4):447-465. (Screening may have begun before the date listed as mandated)

1.3 POLICY REPORTS ON NEWBORN SCREENING

In subsequent years, newborn screening technology continued to evolve and more disorders were included in the State screening panels. Congenital hypothyroidism (CH), a disease more common than PKU, was one of the first disorders to be incorporated into the existing screening programs. Other conditions (e.g., galactosemia, homocystinuria, maple syrup urine disease and sickle cell disease) were also gradually added. As newer techniques became available, policy makers always faced the predicament of which disorders to include in the universal screening panel.[9]

1.3.1 Report by WHO Scientific Group (1968)

Several policy reports have helped shape the newborn screening program as it exists today. In a 2001 review article, Therrell summarized the major policy guidelines on newborn screening. One of the first guidelines on this topic was issued by a World Health Organization (WHO) Scientific Group on Screening for Inborn Errors of Metabolism. A series of five reports was published between 1964 and 1968. The final recommendations of this group touched several aspects of newborn screening that were relevant at that time. The use of suitable technology, automated data analysis techniques, and centralization of the screening process were regarded as important steps towards greater efficiency in the screening system. The group also emphasized the need for research on the incidence of disorders and evaluation of relative efficacy of various screening technologies.[10] A report by Wilson and Jungner was also published in 1968 along with the work by WHO Scientific Group. This report has been frequently used to help guide policy decisions. It highlights the importance of appropriate diagnosis and

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[9] Therrell BL, Jr. U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab.* Sep-Oct 2001;74(1-2):64-74.

[10] Ibid.

treatment options. It also stresses that while it is important to treat the patients who have the disease, it is equally important to avoid harm to those who are unaffected by it. In the next few years, criteria for screening were further refined. Most notably, in his 1974 article, Frankenburg suggested that screening should be conducted for those conditions where early treatment can make significant difference in disease prognosis. Further, for positive cases, adequate resources for treatment should be available; and that in all screening initiatives, the benefits of screening should outweigh the costs.[11]

1.3.2 National Academy of Sciences Report (1975)

In 1975, the National Academy of Sciences published a comprehensive report to assess the current and future challenges in the implementation of genetic screening programs. The highlights of this report were:[12]

1. Screening for any disorder should be backed by evidence of public benefit and acceptance by professionals.
2. Screening should be conducted for conditions where there are established testing techniques and sufficient resources for treatment, counseling and follow-up.
3. The testing process should be within an acceptable range of expenses.
4. Informed consent and patient education should be integrated in the screening program; patients should have the right to refuse screening.
5. Education on topics related to human genetics and its application in various fields should receive priority.
6. New knowledge obtained by screening should contribute to research on finding treatment for disorders that are untreatable.

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11 Ibid.

12 National Academy of Sciences. *Genetic Screening: Programs Principles and Research.* Washington, DC: National Research Council . Committee for the study of inborn errors of metabolism 1975.

1.3.3 The Institute of Medicine (IOM) Report (1994)

Nearly twenty years after the NAS report, the IOM report underscored the importance of informed consent and also gave its stance on mandatory screening:[13]

> Newborn screening only takes place 1) for conditions for which there are indications of clear benefit to the newborn, 2) when a system is in place for confirmatory diagnosis, and 3) when treatment and follow-up are available for affected newborns…
>
> The committee believes that mandatory offering of established tests (e.g., PKU, congenital hypothyroidism) that lead to the diagnosis of a treatable condition, is appropriate. If there is no other way to ensure that affected newborns will be identified and have access to effective treatment (e.g., in PKU, congenital hypothyroidism), then mandatory newborn screening is acceptable…
>
> Mandatory screening should only be undertaken if there is strong evidence of benefit to the newborn from effective treatment at the earliest possible age (e.g., PKU and congenital hypothyroidism).

1.3.4 Report from the Newborn Screening Task Force (2000)

The American Academy of Pediatrics (AAP) organized a Newborn Screening Task Force in 1999. The primary goal of this task force was to assess the problems in state screening programs and to suggest appropriate solutions. The task force sought to address: the role of newborn screening in public health; the status of available systems of care; the economic aspects of screening; the ethical, legal and social implications of screening; and the issues pertaining to research and surveillance.

In its final recommendations, the task force appealed to the public health systems, health professionals and the general public to take action so that the following goals could be accomplished:

1. Federal and State responsibilities are clearly labeled.

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[13] Serving the family from birth to the medical home. Newborn screening: a blueprint for the future - a call for a national agenda on state newborn screening programs. *Pediatrics.* Aug 2000;106(2 Pt 2):389-422.

2. Regulations and minimum standards for newborn screening systems are established.

3. There are clear guidelines for healthcare professionals.

4. There are adequate financial resources to evaluate new technologies, quality of care and health outcomes.

5. The public is involved in the system that provides care to individuals as they go from childhood to adult lives.

1.4 CURRENT STATUS OF NEWBORN SCREENING IN THE UNITED STATES

In the four decades since its inception, newborn screening has evolved into an indispensable part of public health programs in the US as well as many other developed nations. However, screening within the US is by far the most comprehensive. What had started as a single test for detecting PKU has now developed into a multi-dimensional public health initiative. Newborn screening programs are offered by the state departments of health and include the following:[14]

1. Education;
2. Screening;
3. Follow-up and tracking;
4. Confirmatory testing and diagnosis;
5. Disease management; and
6. Quality evaluation and improvement.

Table 1.2 provides a few examples of disorders that are included in most state screening programs.[15] These disorders have been classified as 1) core conditions, 2) core conditions metabolic and 3) secondary target conditions. Details of this classification and screening policies by state are provided in the next section.

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[14] Therrell BL, Adams J. Newborn screening in North America. *J Inherit Metab Dis.* Aug 2007;30(4):447-465.

[15] Kaye C. Newborn screening fact sheets. *Pediatrics* 2006;118:934-963.

Table 1.2 Detailed Information about Disorders Commonly Diagnosed by Newborn Screening

Disorder (American College of Medical Genetics Classification)	**Incidence**	**Manifestations**	**Benefits of screening**
Biotinidase Deficiency: Disorder of biotin (Vit. B) recycling	1/112,000 to 1/129,000	Seizures, hypotonia, dermatitis, alopecia, retarded development, hearing loss	Effective, low cost treatment is available. So, unfavorable outcomes can be avoided
Congenital Adrenal Hyperplasia (CAH): Disorder of adrenal cortex. Impaired cortisol biosynthesis	1/15,981	Adrenal crisis at 3 weeks of age. Vomiting diarrhea, failure to thrive. Mortality for undetected cases 11.9%	Prevention of adrenal crisis, brain damage and death. Prevention of wrong sex assignment in female infants, complications related to excess adrenal androgens
Congenital Hypothyroidism (CH): Deficiency of thyroid hormones	1/3,000 to ¼,000	Slow linear growth after 2-3 months of age, loss of IQ, poor motor skills, speech disorders, cardiac defects, short attention span	Early treatment prevents mental retardation
Cystic Fibrosis (CF): Disease affecting lungs, pancreas, intestine, liver and sweat glands	1/3,500 in Caucasians, 1/7,000 in Hispanics and 1/15,000 in African Americans	Intestinal obstruction, pancreatic insufficiency, respiratory complications, salt imbalance	Early diagnosis and intervention improves height and weight, avoids salt imbalance and improves overall prognosis
Galactosemia: Inability to metabolize a simple sugar galactose (found in breast milk, baby formula and dairy products)	1/40,000 to 1/47,000	Life threatening complications in the first few weeks of life, vomiting, diarrhea, jaundice, hepatomeagly.	A diet free of galactose prevents initial complications. Limited treatment for long term complications
Homocystinuria: Biochemical abnormalities affecting trans-sulfation resulting most often in high concentration of serum methionine	1/300,000; Carriers 1/135	Arterial and renal thrombosis, glaucoma, cataracts, mental retardation, bone and muscle abnormalities	Treatment reduces risk of thromboses, reduces incidence of mental retardation and decreases mortality
Maple Syrup Urine Disease (MSUD): Also called branched chain ketoaciduria. Occurs due to enzyme deficiency	1/85,000 but 1/176 in some communities e.g., Mennonites	Lethargy, poor feeding, weight loss, urine with "maple syrup" odor, seizures, coma, death	Early diagnosis and treatment improves overall prognosis, prevents mortality

Table 1.2 Continued…

Disorder (ACMG Classification)	Incidence	Manifestations	Benefits of screening
Medium Chain Acyl-CoA Dehydrogenase (MCADD): A group of 10 disorders affecting fatty acid oxidation. Often confused with Sudden Infant Death Syndrome (SIDS) or Reye's Syndrome	1/6,400 to 1/46,000 primarily in people of North western Europe	Typically seen between ages of 3-15 months. Severe vomiting and lethargy. Long term complications include developmental problems, speech disorders, muscle weakness, seizures and death	Prevents premature death and reduces the risk of similar problems within a family (There is a 25% chance of recurrence in the same family)
Phenylketonuria (PKU) : Abnormally high blood levels of amino acid Phenylalanine	1/13,500 to 1/19,000	Delayed development, Mental retardation	Inverse relationship between age at diagnosis and IQ. So, very important to screen and diagnose early
Sickle Cell Disease (SCD) and other disorders of hemoglobin: Group of disorders in characterized by chronic hemolysis	1/2,000 to 1/2,500. Especially common in children of African, Mediterranean, Middle eastern, Indian and Central and South American ancestry	Acute muscular or abdominal pain, meningitis, acute chest syndrome or stroke, anemia, jaundice and delayed development.	Prevent mortality because of complications.
Tyrosinemia: Type I characterized by liver dysfunction and Type II characterized by lesions in cornea	Type I 1/100,000 to 1/120,000. Type II: unknown incidence	Type I: vomiting, diarrhea, hepatomeagly, jaundice, failure to thrive. Type II: Disorders of the eye; various abnormalities of cornea, conjunctivitis.	90% patients respond to treatment and this helps reduce mortality from liver failure

Adapted from: Kaye, C., and the Committee on Genetics. Newborn screening fact sheets.

Pediatrics 2006; 118: pp 934-963

1.5 Screening Via Tandem Mass Spectrometry

Tandem Mass Spectrometry (MS/MS) is one of the most important advances in newborn screening in the recent years. Inborn errors of metabolism can cause one or more enzymes to have limited activity or to be completely absent. In the absence of those enzymes, the newborn's body is unable to breakdown amino acids or fats. As a result, these compounds tend to accumulate in the blood and other tissues. A tandem mass spectrometer is capable of weighing amino acids and acylcarnitines (a fatty acid molecule attached to a transportation system called carnitine) found in a blood sample. It also calculates the amount of each of these molecules and displays the results in the form of vertical lines plotted on a horizontal axis called the mass spectrum. The position of vertical lines along the spectrum helps identify the mass of the molecule and the height of the line corresponds to its quantity in the sample. This information can help detect the presence of one or more metabolic errors. (See Appendix A for a detailed view of images generated by MS/MS).

1.6 State Screening Programs and Conditions Detected by Screening

Although newborn screening has been in place for more than forty years in the US, there are huge discrepancies in screening programs by state. Variability in screening may arise due to differences in prevalence of a disorder, availability of treatment, accuracy of testing, cost-effectiveness of screening and overall budgetary decisions of a state. The list of disorders screened in one state is not representative of the conditions covered in other states. The conditions covered by screening are divided into three categories by the American College of Medical Genetics (ACMG):

1. **Core Conditions:** These include hearing disorders, endocrine disorders like Congenital Hypothyroidism (CH) and Congenital Adrenal Hyperplasia (CAH),

disorders of hemoglobin such as Sickle Cell Disease (SCD), biotinidase deficiency, galactosemia, and Cystic Fibrosis (CF). Of all these disorders, screening is uniformly required by law for only CH, hemoglobin disorders (SCD and others) and galactosemia in all the states. Hearing screens are required by law in some states but in others they are either universally *offered* but not *required* and in some others, they are offered only to select populations. Biotinidase screening is required in most states but there are a few cases where it is offered to select populations or is not yet implemented.

2. **Core Conditions – Metabolic:** These include fatty acid disorders such as Medium-chain Acyl-CoA Dehydrogenase (MCADD), organic acid disorders such as Glutaric Acidemia (GA), and amino acid disorders such as PKU. Of the entire list of metabolic disorders, only screening for PKU is universally required by law in all the states. According to the latest data from the National Newborn Screening and Genetic Resource Center (NNSGRC), testing for core metabolic conditions is required but not yet implemented in a few states namely Arkansas, Kansas, Montana and West Virginia. Pennsylvania offers screening for most core metabolic disorders but only to select populations. This policy may have been enacted for the benefit of certain native communities like the Amish and Mennonites. The incidence of many inborn errors of metabolism (e.g., MSUD and Glutaric Acidemia) is especially high in these communities due to inbreeding.[16]
3. **Secondary Target Conditions:** These include additional fatty acid disorders, organic acid disorders and amino acid disorders. There is tremendous variation in state programs with respect to this category of disorders. Screening for a certain

[16] Morton DH, Morton CS, Strauss KA. Pediatric medicine and the genetic disorders of the Amish and Mennonite people of Pennsylvania. *AmJ Med Genetics.* 2003;121C(1):5-17.

secondary target condition may be required by law in one state but in others, it may not yet be implemented and in still others, it may be offered only to select populations.

The National Newborn Screening and Genetic Resource Center (NNSGRC) periodically updates the national newborn screening status report at its website. A copy of the most recent screening status report is included in Appendix B.

1.7 NEWBORN SCREENING EXPENDITURE AND THE ROLE OF MEDICAID

More than one-third of the births in the US are financed by Medicaid. These newborns are automatically eligible for Medicaid which covers screening and follow-up expenses. The Early and Periodic Screening, Diagnosis and Treatment (EPSDT) program is also a part of Medicaid which provides special diets, hearing aids and therapies for infants who are diagnosed with one or more genetic disorders during screening.[17]

A report from the General Accounting Office (GAO) has detailed information on the expenses incurred by newborn screening programs in each state. Surveys conducted on individual states revealed that there was a great deal of variation in screening expenses incurred by various states. In fiscal year 2001, individual states spent anywhere from $87,000 to $27 million on newborn screening. States reporting very high expenditures had made capital investment such as procuring equipment for tandem mass spectrometry (MS/MS testing). Many states reported significant increase in their fee for newborn screening in the last few years primarily due to program expansions. On average, states spent $29.44 per child in their screening programs. Forty-three of the fifty states charged a screening fee from the health care provider. The providers were later reimbursed by

[17] Serving the family from birth to the medical home. Newborn screening: a blueprint for the future - a call for a national agenda on state newborn screening programs. *Pediatrics.* Aug 2000;106(2 Pt 2):389-422.

Medicaid or private health insurance. In the remaining seven states, Medicaid was directly responsible for the financial burden of offering screening.[18] A more detailed account of trends in newborn screening fee by state is provided in Appendix C.

1.8 SCREENING IN TEXAS

The state of Texas has several unique attributes: it is the second most populous state in the country and has the second highest birth rate. It ranks third in both the percent of persons below the poverty level and the number of residents younger than 18 years. Texas also has the highest uninsured population. These statistics pose tremendous challenges especially in light of the fact that Texas ranks 45th in terms of per capita government expenditures. The demographics related to newborns are also equally daunting. About 6,600 babies are born every week in Texas. Of these, 1,000 are born to mothers receiving suboptimal prenatal care and 500 record a low birth weight. The death rate for children younger than 1 year is about 50 per week.[19]

Texas began newborn screening with a pilot program to screen for PKU in 1963. After the success of the pilot program, a 1965 statute mandated population-wide PKU screening in the state. In the subsequent years, the screening program saw gradual expansion to five conditions. Table 1.3 provides a brief history of screening within the state of Texas.

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18 US General Accounting Office. Newborn Screening: Characteristics of State Programs; 2003:1-47.

19 National Newborn Screening and Genetics Resource Center. *Consultation Report Texas Newborn Screening Program.* Austin, Texas February 28 - March 2, 2005 2005.

Table 1.3 History of Newborn Screening in Texas

Condition	Year Screening Was Initiated	Annual Incidence Within Texas
Phenylketonuria (PKU)	1965	1:34,349
Galactosemia	1978	1:76,505
Congenital Hypothyroidism (CH)	1980	1:2,404
Sickle Cell disease	1983	1:350 (in African Americans) 1:37,000 (in others)
Congenital Adrenal Hyperplasia (CAH)	1989	1:16,664

In 2004, the Texas Newborn Screening Program reported to have received 756,130 specimens (approximately 3,000 per day). This number is almost twice the number of live births in 2004 (approximately 375,000). This is because Texas requires all newborns to undergo two screens – with the first specimen collected between 24-48 hours of age and the second specimen collected between 1-2 weeks of age. Therefore, the influx of specimens sent to the newborn screening laboratory includes specimens for first screens, specimens for second screens and also some specimens for repeat screens for previously unsatisfactory specimens. According to Texas Department of State Health Services (DSHS) estimates, 95% of newborns receive their first screen, and 90% receive both their first and second screens.[20]

The newborn screening program in Texas has two sections: the specialized health services section and the laboratory services section. The specialized health services section is comprised of the administrative, follow-up and educational services and is a part of the Division for Family and Community Health Services. On the other hand, the laboratory services section includes the newborn screening laboratory. In 2004, the administrative, follow-up and educational services received annual funding of about

[20] Ibid.

$700,000 from Medicaid and Title V Maternal and Child Health Block Grant funds. The laboratory services section is financed via a fee-for-service plan. This section generated annual revenue of $14 million through charging fees for laboratory services and through the sale of newborn screening kits. The fee charged for Medicaid patients was $16.20 per specimen and that for non-Medicaid patients was $19.50 per specimen in 2004. Medicaid reimbursed the laboratory for providing services to Medicaid eligible patients.[21]

1.8.1 House Bill 790

In response to recommendations from agencies like the March of Dimes and the American College of Medical Genetics (ACMG), the State of Texas passed House Bill 790 (HB 790) in 2005 which required the Department of State Health Services (DSHS) to implement expanded testing (which includes 27 of the 29 recommended tests) by November 1, 2006.[22] According to the ACMG, all newborns should be screened for 9 Organic Acid Metabolism Disorders, 5 Fatty Acid Oxidation Disorders, 6 Amino Acid Metabolism Disorders, 3 Hemoglobinopathies and 6 disorders that fall under the "other" category. After the expansion, 19 disorders detected by MS/MS and biotinidase deficiency were added to the existing screening panel in Texas. The expansion of benefits also included dietary supplements, medications, vitamins, confirmatory testing and follow-up care for eligible newborns. It was estimated that after the expansion, DSHS laboratory would receive approximately 800,000 specimens a year. Follow-up would be required for about 15,000 abnormal screens. Of these, 600 screens would result in confirmed core disorders and another 300 may be confirmed for variant or other

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21 Ibid.

22 House Bill 790. http://www.capitol.state.tx.us/tlo/79r/billtext/HB00790F.HTM. Accessed June 23, 2006.

disorders.[23] HB 790 has allocated $7.4 million for providing expanded screening in Texas. Details of HB 790 can be found at: http://www.capitol.state.tx.us/tlo/79r/billtext/HB00790F.HTM.

1.8.2 Overview of the Newborn Screening Process

Although each state may differ in terms of the number of disorders included on the screening panel, the overall screening process is very similar. When a newborn is 24-48 hours old, a simple heel prick is used to draw a blood sample. This sample is transferred onto a two dimensional filter paper (not in a vial). The filter paper is a part of the newborn screening kit and includes space for the demographic information of the infant. An example of the specimen collection form is shown in Appendix D. After being dried for at least four hours, the filter paper is mailed to the state laboratory. The state laboratory then uses the dried blood sample for testing purposes. Many states, including Texas, also require a second screen at the age of 1-2 weeks. The purpose of the second screen is to avoid false negative results. With tandem mass spectrometry (MS/MS), it is now possible to test the same blood sample for about 50 disorders. If a test result is found positive, the laboratory staff immediately notifies the case management staff. The case management staff is responsible for conveying the infant's screening results to the physician's office in a timely manner since some disorders can be fatal within the first few days of life. The case management staff also maintains up-to-date "FACT SHEETS" and "ACT SHEETS" for each of the disorders. The fact sheets contain a description of the disorder and the act sheets contain information on the immediate medical interventions that may prevent morbidity or mortality in the affected infant. Appendix E

[23] Drummond-Borg M. Newborn Screening. Saving lives, improving outcomes. Austin, TX: Texas Department of State Health Services; 2006.

provides an example of an abnormal test result. Appendix F and G provide examples of the fact and act sheets.

The physician's office then notifies the infant's family. The family is given instructions on dietary restrictions, confirmatory testing and any hospitalization if necessary. For example, a positive result for galactosemia means that the infant is unable to metabolize the milk sugar galactose. Within the first few days of life, a galactosemic infant may present in the emergency room with jaundice, vomiting, poor feeding and bacterial infections. Upon receiving a presumptive positive screening result for galactosemia, the infant's family is instructed to immediately stop feeding the baby with breast milk or infant formula and replace it with a soy-based diet. This change in diet usually results in dramatic improvement in the infant's health and survival. After the initial notification of a positive screening result, case management also ensures regular follow-up of positive children.

1.9 CRITICISM AGAINST NEWBORN SCREENING

With rapid advances in human genetics and screening techniques, it is now possible to screen an infant for a large number of disorders. However, critics believe that policy makers and the general public have an overly optimistic view of screening. False positive results, lack of adequate treatment options and unavailability of confirmatory testing can lead to tremendous ethical, social and legal implications.

In a 2006 article, Tarini et al. estimated the impact of false positive test results in newborn screening using birth statistics for 2004. They reported that using a base estimate of 99.95% specificity for confirmatory testing for newborn screening disorders, approximately 25,644 infants would receive a false positive result in one year in the US.

Using a best case scenario of 99.995% and a worst case scenario of 99.9%, the number of false positives could range from 2,575 to 51,059 every year.[24]

Some researchers have examined the long-lasting impact of false positive results on a child and his family. It has been reported that in spite of subsequent testing that may confirm that the child is healthy, parents tend to remain stressed and overly protective of a child with a history of a false positive diagnosis. When compared with that of children with normal screen results, hospitalization rates tend to be higher in the false positive group. [25]

While newborn screening may provide significant benefit to the truly affected child, it can bring unintentional harm to the false positive child and his family. Since many of these disorders are rare, the number of false positives may frequently exceed the number of true positives.

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[24] Tarini BA, Christakis DA, Welch HG. State Newborn Screening in the Tandem Mass Spectrometry Era: More Tests, More False-Positive Results. *Pediatrics* 2006;118:448-456.

[25] Waisbren SE, Albers S, Amato S, et al. Effect of expanded newborn screening for biochemical genetic disorders on child outcomes and parental stress. *JAMA.* Nov 19 2003;290(19):2564-2572.

Chapter Two – Economic Studies of Newborn Screening

2.1 INTRODUCTION

Since the widespread adoption of newborn screening in the 1960s, policy makers and State Departments of Health have tried to strike a balance between offering the latest diagnostic techniques and economic viability. At present, it is possible to screen newborns for more than 50 disorders. Yet, most newborn screening programs offer population-wide screening for only 29 of those conditions. Among other issues such as sensitivity and specificity of the screening test, and treatment options for positive cases, cost-effectiveness of screening is also a major factor that determines the inclusion of a diagnostic test in the screening panel.

2.2 TYPES OF ECONOMIC ANALYSES USED TO ASSESS NEWBORN SCREENING

Numerous studies have been conducted to evaluate the economic aspects of newborn screening. Most frequently, authors have performed cost-benefit, cost-effectiveness and cost-utility analyses. A brief description of each of these analyses is provided below.

2.2.1 Cost-benefit Analysis (CBA)

Cost-benefit analysis (CBA) is a type of analysis where all the resources utilized (costs) for providing a treatment or intervention are compared with its usefulness (benefits). In CBA, monetary values are assigned to both benefits and costs. Net benefit is calculated by finding the difference between total costs and total benefits. A treatment option is considered economically viable when the benefit-to-cost ratio exceeds 1.0.[26]

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[26] Bootman JL, Townsend RJ, McGhan WF. *Principles of Pharmacoeconomics*. Third ed. Cincinnati, OH: Harvey Whitney Books Company; 2005.

2.2.2 Cost-effectiveness Analysis (CEA)

For cost-effectiveness analysis (CEA), the resources consumed (costs) for providing an intervention are compared with its outcome that is measured in natural units. CEA differs from CBA in that it does not assign monetary values to treatment outcomes. Instead, outcomes may be measured in "real-life" units like number of symptom-free days or years of life saved. The ratio of differential cost to that of the differential effectiveness (when comparing two treatment options) is called the incremental cost-effectiveness ratio (ICER).[27]

2.2.3 Cost-utility Analysis (CUA)

Often considered a special case of CEA, cost-utility analysis examines the cost of a treatment relative to its effect that is measured in quality adjusted life years (QALYs). QALYs represent the quantity and the quality of life in a single unit. For example, each year of life lived in perfect health is assigned a value of 1.0 while death is assigned a value of 0. A disease state may be represented on this continuum by a value that is greater than 0 but less than 1.0.[28] QALYs are preferred over Life Years (LYs) as an outcome measure because they reflect morbidity and mortality versus mortality alone.

2.3 Lack of Uniformity in Economic Studies of Newborn Screening

Economic analysis of newborn screening strategies is a relatively new concept that has been continually evolving. It is common to encounter contradictory findings in the literature, especially while comparing newer studies with relatively older ones. It is very important to be cognizant of the context in which each of the studies was done. Several factors contribute to the lack of uniformity found in the literature:

1. Difference in alternatives being compared.

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[27] Ibid.
[28] Ibid.

2. Conditions included (or excluded) in the analysis.
3. Different coverage policies in different states.
4. Disparate discounting rates used in some of the older studies.
5. Different outcome measures used in older studies. For example, some measures of outcomes such as Quality Adjusted Life Years (QALYs) are not used in older studies.
6. Continuous evolution of screening technologies.

The results of specific economic studies are summarized in this chapter.

2.4 THE OFFICE OF TECHNOLOGY ASSESSMENT (OTA) REPORT

A 1988 report was published by the Office of Technology Assessment (OTA) in response to a Congressional committee request for an assessment of cost-effectiveness of preventive measures for infants and children. Newborn screening was one of the measures evaluated, in addition to prenatal care, well child care, accidental injuries and child abuse.[29]

In their literature review, the OTA referred to some of the older studies that had evaluated the costs of Phenylketonuria (PKU) screening and some others that had examined the costs of screening for Congenital Hypothyroidism (CH). Other studies that had evaluated the effectiveness of simultaneous screening for several disorders were also discussed. Most of these studies had weighed the costs of screening against the benefits of avoiding unfavorable outcomes and pointed to the general usefulness and cost saving effect of newborn screening.[30]

The OTA asserted that their study was unique since it was studying the effect of collecting blood samples for a second screen. They contended that the results of previous

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29 Office of Health Technology Assessment (OTA). *Healthy Children: Investing in the Future* 1988.
30 Ibid.

studies were misleading because many important factors like costs of specimen collection and long-term follow-up were omitted.[31]

The OTA study compared seven strategies: the basic strategy of one specimen screening for Phenylketonuria (PKU) and Congenital Hypothyroidism (CH) and six other strategies that had one or two specimen collection points and screening for various combinations of PKU, CH, homocystinuria, galactosemia, and Maple Syrup Urine Disease (MSUD). The basic strategy of screening all newborns for PKU and CH by collecting a single specimen yielded cost savings of $3.2 million/100,000 infants. The combined rate of PKU and CH cases identified with screening was 34/100,000 infants screened. These numbers translate into an average cost saving of $93,000 per case. Results of sensitivity analyses showed that these savings could range from $110,000 to $22,000 in best and worst case scenarios, respectively. Assuming a screening rate of 3.7 million newborns per year, national savings using the basic strategy could amount to $120 million annually. However, the results for other strategies were not that encouraging. The OTA reported that if specimens were collected twice or additional disorders were included in screening, then incremental costs could range from $253,000 to $466,000 for detection and treatment of each additional case. OTA suggested that additional screening (beyond PKU and CH) was a costly prospect and states should rely on very strong empirical evidence before including any additional tests in their screening panels.[32]

2.4.1 Critique of the OTA Study

In a 2004 advisory committee meeting on heritable disorders and genetic diseases in newborns and children, the OTA study was critiqued and it was pointed out that many

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31 Ibid.
32 Ibid.

of the results of this study were not relevant anymore. Specific points made by the advisory committee were: the outcome measure used in the OTA study (number of cases detected) was obsolete; if healthy life years saved were used as an outcome measure, then the cost of screening would not be high; the study had used a discount rate of 7% whereas most modern studies use a rate of 3%; above all, the analysis involves older screening technologies which were far less effective than the current technologies.[33]

The advisory committee also maintained that it is crucial to recognize additional factors that may help in obtaining robust analyses. In many states, a full range of tests is not covered by public health agencies and private laboratories play an important role in screening. Therefore, the costs incurred by these laboratories should be considered. The capital investment for tandem mass spectrometry (MS/MS) equipment and specialized training of current employees also needs to be included in the analysis.[34]

2.5 RECENT STUDIES

Studies conducted in the last 10 years (1997-2007) have examined the economic implications of newborn screening with MS/MS. Some of the studies have included only one or two disease states while others have incorporated the effect of screening for multiple conditions in a single test. Decision tree analysis or Markov Modeling is frequently used for assessing the cost-benefit ratio or cost-effectiveness of screening. The costs included in a study can be categorized as program implementation costs, direct medical costs and direct non-medical costs. Examples of costs incurred in establishing a population-wide screening program often includes the cost of screening (incremental cost of offering MS/MS), personnel, equipment, supplies, laboratory contracts, follow-up

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33 Wagner J, Ostrowsky J. *OTA's newborn screening study: relevance to today's issues.* Washington, DC Second advisory committee on heritable disorders and genetic diseases in newborns and children; September 2004.

34 Ibid.

testing of false positives, and quality control for laboratories. Other medical costs include inpatient, outpatient and emergency visits as well as the physician fees. Non-medical costs include transportation expenses and wages lost by both parents. An annual discount rate of 3% is used by most authors.

Utility values ranging from 0 (for death) and 1 (for perfect health) are used as a qualitative measure to simultaneously reflect morbidity and mortality. When utility values are multiplied by the number of years in each health state the resulting number is termed Quality Adjusted Life Years (QALYs). Timely detection of metabolic errors can increase QALYs by 0.7 to 0.8 per year. On the other hand, false positive results can lead to a disutility of -0.01 to -0.03 (annualized). Since there is no documentation of the disutility caused by a false positive result in newborn screening, these estimates are based on the disutility of a false positive result in cancer studies. It may be argued that such an estimate may not be an accurate representation of the disutility caused by a false positive newborn screen result because of the unique circumstances involving a newborn and his/her family. Many other factors also need to be accounted for in a modeling study. Prevalence of a condition, proportion of asymptomatic patients, sensitivity and specificity of a diagnostic test, risk of mortality, and cost of confirmatory tests after an initial positive screen are all important variables that can affect the final result of a cost-effectiveness study.[35] [36]

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[35] Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

[36] Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol.* Sep 15 2000;18(18):3302-3317.

2.6 INTERNATIONAL STUDIES ON ECONOMICS OF NEWBORN SCREENING

Newborn screening is conducted routinely in Europe and some other developed nations although the number of disorders included in the screening panel varies across countries. The exchange rates for the following studies were: 1Great Britain Pound (GBP)=0.61United States Dollar (USD) in 1997; 1GBP=0.54 USD in 2004 and in 2006.[37] The author used these exchange rates to calculate the appropriate values of USD from GBP.

In a 1997 study conducted in the United Kingdom (UK), Pollitt et al. examined the costs and benefits of newborn screening with MS/MS**.** They used a decision analytic model to compare cost per additional case identified, additional treatment costs per case for each disorder, and the cost per life-year saved. They used a discount rate of 6% per annum (versus the current practice of 3% per annum). Study results showed that for an annual workload of 100,000 samples, a marginal cost of £0.60 (0.98 USD) per sample would be incurred if the old screening technology was replaced by MS/MS. For an annual workload of 50,000 samples, the marginal cost would go up to £0.87 (1.41USD) per sample. An expansion of the screening program would increase the number of positive cases detected, which in turn would result in additional laboratory expenses. The authors concluded that an expansion of the existing screening program (which included PKU and Congenital Hypothyroidism) would result in overall marginal costs of £18,000 (29,340 USD) per year in the short run and £174,000 (283,620 USD) per year in the long run. Population-wide screening of MCADD was declared as a financially viable option with a treatment cost of £31(51 USD) per life year saved. However, screening for other

[37] FX History: historical currency exchange rates. http://www.oanda.com/convert.fxhistory. Accessed September 15, 2007.

disorders such as tyrosinemia were not as financially attractive with a treatment cost of £8,339 (13,593 USD) per life year saved.[38]

In an attempt to evaluate the cost-effectiveness of replacing the existing screening technology with MS/MS, Pandor et al. reported in 2004 that the use of MS/MS for PKU screening alone was not a rational choice. However, if MCADD screening were added to the panel, then for an estimated range of 50,000 to 60,000 specimens annually, the incremental cost of screening would be -£23,312 (43,170 USD). Additionally, for every 100,000 newborns, an average of 59 life-years would be gained.[39] These results were reinforced in a follow-up study conducted in 2006. The authors reported that if MS/MS were used for screening for PKU and MCADD, then incremental costs of screening were estimated to be - £17,298 (-31,655 USD) [CI -£129,174 (-236,388 USD), to £66,434 (121,574 USD)] per 100,000 newborns. These savings are associated with a mean incremental gain of 57.3 (CI 28.0, 91.4) life years indicating that this is a dominant choice.[40]

These results are encouraging and in line with the current scope of MS/MS screening. All states in the US are adopting MS/MS for simultaneous screening of multiple disorders.

2.7 STUDIES CONDUCTED IN NORTH AMERICA (UNITED STATES AND CANADA)

Table 2.1 provides a brief description of some recent (2002-2007) economic analyses performed in North America. These studies have examined the economic

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38 Pollitt RJ, Green A, McCabe CJ, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. *Health Technol Assess.* 1997;1(7):i-iv, 1-202.

39 Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S. Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review. Ibid.Mar 2004;8(12):iii, 1-121.

40 Pandor A, Eastham J, Chilcott J, Paisley S, Beverley C. Economics of tandem mass spectrometry screening of neonatal inherited disorders. *Int J Technol Assess Health Care.* Summer 2006;22(3):321-326.

viability of various screening strategies and in general, form a consensus that newborn screening is a cost-effective intervention.

Table 2.1 Summary of Recent Economic Analyses of Newborn Screening in North America

Year (Section)	Author(s)	Type of Analysis	Conditions Studied	Main Findings
2002 (Section 2.2.2.1)	Schoen, Baker, Colby and To[41]	CUA	MSUD, MCADD, Glutaric Aciduria, MMA, PPA, Urea cycle disorders, Homocystinurea	MS/MS yields an ICER of $5,827/QALY
2002 (Section 2.2.2.2)	Insinga, Laessig and Hoffman[42]	CUA	MCADD and other fatty acid disorders	MS/MS yields a ICER of $6,008/QALY
2003 (Section 2.2.2.3)	Venditti, Venditti, Berry et al.[43]	CEA, CUA	MCADD	MS/MS screening for MCADD requires an additional $5,600/QALY ($11,000/LY) as compared to no screening.
2006 (Section 2.2.2.4)	Carroll & Downs[44]	CUA	PKU, CAH, CH, MSUD, Galactosemia, Homocystinuria, MCADD, biotinidase deficiency	Multi-test screening is dominant approach in all disorders except CAH and Galactosemia
2006 (Section 2.2.2.5)	Feuchtbaum & Cunningham[45]	CEA, CBA, CUA	MS/MS detectable disorders other than PKU	MS/MS screening saves $1.5 million annually. Screening is the dominant strategy in CBA and CUA
2007 (Section 2.2.2.6)	Tran, Banerjee, Li et al.[46]	CEA, CUA	MCADD	Screening for MCADD with MS/MS is cost-effective based on a threshold value of $20,000 per QALY

41 Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* Oct 2002;110(4):781-786.

42 Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Pediatr.* Oct 2002;141(4):524-531.

43 Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

44 Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Ibid.May 2006;117(5 Pt 2):S287-295.

45 Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Ibid.:S280-286.

46 Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, Dooley K. Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin Biochem.* Feb 2007;40(3-4):235-241.

2007 (Section 2.2.2.7)	Cipriano, Rupar, Zaric[47]	CEA	PKU and 14 other disorders	Average cost of screening for PKU, along with 14 other disorders is $95,000 per life year gained.

Abbreviations used: CBA=Cost-benefit Analysis, CEA= Cost-effectiveness analysis, CUA= Cost-utility Analysis, PKU=Phenylketonuria, MCADD= Medium Chain Acyl Co-A Dehydrogenase Deficiency, CAH= Congenital Adrenal Hyperplasia, CH=Congenital Hypothyroidism, MS/MS=Tandem Mass Sprectrometry, QALY=Quality Adjusted Life Year, MMA= Methylmalonic Acidemia, PPA=Propionic Acidemia.

2.7.1 Schoen et al. (2002)

In a 2002 study on universal newborn screening using MS/MS, Schoen et al. examined the costs and benefits of the program in a California-based Health Maintenance Organization (HMO). Under the costs of screening, the authors included cost of screening, cost of hospital stay, cost of special diet and treatment costs for the first five years of a child's life. Whenever appropriate, these costs were compared for early versus late detection of inborn errors of metabolism (IEMs) (Table 2.2). In addition, an average cost of $1,000 was assigned to each false positive result for various IEMs. This cost included the cost of test itself, follow up by a genetics nurse, visit to an urgent care clinic, confirmatory lab tests, visit to the emergency room (ER) and/or hospital stay (Table 2.3). The only exception was MCADD where the cost of a false positive result was estimated at $200 since no immediate medical treatment is warranted in this case.[48]

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47 Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

48 Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* Oct 2002;110(4):781-786.

It was estimated that in the base case scenario, screening would cost $5,827/QALY with a range of $736 to $11,419/QALY for the best and worst case scenarios respectively (Table 2.4).

Table 2.2 Estimated Base Costs Associated with Newborn Screening – Schoen et al.[49]

Cost Category	Estimated Value
Cost of screening	$15
Hospital stay (early detection)	$4,000
Hospital stay (late detection)	$8,000
Five-year treatment cost (early detection)	$64,116*
Five –year treatment cost (late detection)	$93,884**
Cost of special diet for patients younger than 5years	$10,000
Cost of special diet for patients older than 5years	$2,500

*=assumed $0 for MCADD; **=Assumed $0 for MCADD and $118,884 for MSUD

Table 2.3 Estimated Costs of False-Positive Test Results – Schoen et al.[50]

Cost Category	Estimated Value
Response by genetics nurse	$100
Visit to urgent care	$110
Laboratory tests	$600
Visit to ER	$200
Hospital stay	$2,000

49 Ibid.
50 Ibid.

Table 2.4 Cost Per Quality Adjusted Life Year Saved by Screening – Schoen et al.[51]

Scenario	Cost/Patient	QALY/Patient	Cost Per QALY
Base Case	$15.49	0.0026	$5,827
Least Favorable	$27.39	0.0024	$11,419
Most Favorable	$2.23	0.0028	$736

2.7.2 Insinga et al. (2002)

In an incremental cost-utility study on a hypothetical cohort of 100,000 infants, Insinga et al. examined the impact of introducing MS/MS screening in Wisconsin. The authors focused only on the outcomes of being able to screen for MCADD using MS/MS. There are several reasons why a number of studies have been conducted on this one disorder: MCADD is a relatively common metabolic error having an incidence rate similar to that of PKU (approximately 1 in 11,000 to 1 in 15,000); MS/MS screening offers a high degree of sensitivity (0.95 to 1.0) and specificity (0.995 to 1.0) for MCADD detection; if detected early, it is a highly treatable disorder with very good patient outcomes.[52] Screening for MCADD is therefore expected to provide a relatively high benefit from a societal perspective.

In this study, costs pertaining to incremental cost of screening, confirmation of positive or negative screening test, special diet for a life-time, follow-up testing and physician visits, hospital admission and possible neurological impairment were included. Confirmatory testing for a positive screen may involve additional tests to determine the

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51 Ibid.

52 Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Pediatr.* Oct 2002;141(4):524-531.

exact genetic basis of the disease. A breakdown of base-case cost estimates is shown in Table 2.5.

Table 2.5 Base Case Cost Estimates – Insinga et al. [53]

Cost Category	**Estimated Value**
Incremental cost of MS/MS screening	$3.99
MS/MS test confirmation (positive for MCADD)	$1,715
MS/MS test confirmation (negative for MCADD)	$1,465
Added lifetime carnitine supplementation cost per child	$10,678
Added lifetime follow-up testing and visit cost per child	$12,427
Cost per routine hospital admission	$2,833
Cost per case of neurologic impairment	$552,000

Assuming utility values of 0.06 and 0.67 with severe and mild neurological impairment respectively, the study included QALYs gained as the outcome measure. Results of the cost-utility analysis showed that the net cost of screening for MCADD alone was $401,879 with a total gain of 9.6 QALYs. This yields an incremental cost-effectiveness ratio (ICER) of $41,862/QALY which is below the threshold of $50,000/QALY as per the established practice for assessing the effectiveness of a new intervention (Table 2.6). In practice, the newborn screening panel would include more disorders which would result in a lower cost per QALY.[54]

[53] Ibid.
[54] Ibid.

Table 2.6 Base Case Cost-effectiveness Estimates – Insinga et al.[55]

Cost Category	Estimated Value
Total Costs	$526,079
Cost Savings	-$124,200
Net cost of screening for MCADD	$401,879
QALYs gained from prevented deaths	5.8
QALYs gained from prevented severe neurological impairment	2.8
QALYs gained from prevented mild neurological impairment	1.0
Total QALYs gained from screening	9.6
Cost-effectiveness Ratio	$41,862/QALY

2.7.3 Venditti et al. (2003)

In a simulation study using primary data from retrospective chart reviews, patient/family interviews, expert opinion and secondary data from the literature, Venditti et al. tracked the outcomes of screening of infants from birth through adulthood. Their primary model made predictions for the first twenty years of life and then another simulation studied the outcomes until 70 years.[56] The model included cost of screening, cost of follow up and confirmatory tests for presumptive positive patients, treatment for MCADD and related complications, inpatient, outpatient and emergency room visits (Table 2.7).

55 Ibid.

56 Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

Table 2.7 Costs Incurred in Screening (range used in sensitivity analyses) – Venditti et al.[57]

Cost Category	Estimated Value
Screening and follow up by newborn screening program	$4 ($1-$20)
Confirmatory testing for final diagnosis of a positive screen result	$2,120 ($0-$5,000)
Carnitine treatment for patients diagnosed with MCADD	$0 ($0-10,000)
Care for severely affected	$1,914 ($0-$4,000)

It was assumed that the utility of being healthy was 1.0 and the utility of being diagnosed with MCADD via screening and confirmatory testing was also very close to 1.0 (0.99). Utility for unscreened patients who were diagnosed on the basis of symptoms was estimated at 0.88 and that for undiagnosed patients was estimated at 0.65. Annualized disutility of a false positive was estimated to range between -0.01 and -0.03. Although no formal studies have been performed to assess the disutility of false positives in metabolic disorders, results from cancer studies were used to estimate the disutility of the anxiety caused by a false positive MCADD diagnosis. [20]

Threshold values for C/E ratios were also based on reports in the literature. Results of the study showed that over a period of 20 years, the cost of newborn screening for MCADD was $5,600 per QALY (Table 2.8). Simulation modeling at a 70-year horizon showed that MCADD screening cost only $100 per QALY. These results indicate that over a longer term, screening is a very cost-effective measure. [20]

[57] Ibid.

Table 2.8 Base case Cost-effectiveness and Projections on a 20 year Horizon for the 2001 US Newborn Cohort (4,040,121 infants) – Venditti et al.[58]

Variables	With Screening	Without Screening	Difference
Total cost	$19,009,981	$13,485,520	$5,524,461
Total effectiveness (LYs)	57,951,023 LYs	57,950,522 LYs	501 LYs
Total effectiveness (QALYs)	57,950,983 QALYs	57,949,993 QALYs	990 QALYs
Average cost per neonate	$4.7053	$3.3379	$1.3674
Average effectiveness per neonate (LYs)	14.343883 LYs	14.343759 LYs	0.000124 LYs
Average effectiveness per neonate (QALYs)	14.343873 QALYs	14.343628 QALYs	0.000245 QALYs
Incremental cost-effectiveness ratios : Cost/LY saved (95% CI) = $11,000 Cost/QALY saved (95% CI) = $5,600			

2.7.4 Carroll and Downs (2006)

In a 2006 study on the cost-effectiveness of including a broad MS/MS testing into a newborn screening program, a comparison was drawn between individual screening tests for seven metabolic disorders and simultaneous screening with MS/MS. Assuming that the MS/MS screening panel would include PKU, biotinidase deficiency, MSUD, galactosemia, MCADD and homocystinuria, the authors compared three alternative strategies: no screening; screening with MS/MS; and screening with individual tests designed to detect PKU, CAH, CH, biotinidase deficiency, MSUD, galactosemia and homocystinuria.[59]

Table 2.9 shows the costs incurred when each of the disorders is screened individually or simultaneously (using MS/MS). The study took a societal perspective and included start up costs, operating costs, life-time treatment costs and costs of sequeale. Estimates of life-time treatment costs for each of the disorders and the costs of common

58 Ibid.

59 Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. May 2006;117(5 Pt 2):S287-295.

sequeale of are shown in Tables 2.10 and 2.11 respectively. These tables also include the threshold values (obtained from sensitivity analysis) at which the tests are "no longer cost saving". In the decision analysis, a "multiplicative utility model" was used where utilities of all the possible complications were multiplied to account for >1 complications in the possible outcomes. Life expectancy estimates for disabilities were derived from the literature.

A comparison was drawn between various screening strategies and not screening. Results showed that a combined screening panel with MS/MS was the most dominant strategy where the incremental cost of screening was -$43 per screen. Even when individual screening tests were performed for each of the disorders, screening still dominated the "no screening" strategy. The only exceptions were testing for CAH and GAL which cost $20,000 per QALY gained and $94,000 per QALY gained, respectively. However, if a conventional benchmark of $50,000 per QALY gained is used, then even the CAH test would be deemed cost-effective. MS/MS screening was found to be the least expensive screening method (Table 2.12).[60] Like most other studies, this study also underscored the importance of sensitivity and specificity of the screening method since false positive results can lead to substantial costs. A high false positive rate ultimately translates into lack of cost-effectiveness.

[60] Ibid.

Table 2.9 Cost Comparison of Various Screening Tests – Carroll and Downs[61]

Type of Screening Test	**Base Case Costs ($)**	**Threshold Values obtained from Sensitivity Analysis**
Biotinidase	$1.83	$14.00
Congenital Adrenal Hyperplasia	$3.63	Not listed
Congenital Hypothyroidism	$4.59	$8.70
Galactosemia	$3.79	Not listed
Homocystinurea	$0.84	$2.45
Maple Syrup Urine Disease	$2.49	$2.90
Phenyl Ketonurea	$3.43	$38.20
MS/MS	$16.02	$58.00
Follow-up (any false positive)	$300.00	Range $600 to $10,000

Table 2.10 Lifetime Cost of Treatment of Various Inborn Errors of Metabolism – Carroll and Downs[62]

Name of Disorder	**Base Case Costs ($)**	**Threshold Values Obtained from Sensitivity Analysis**
Biotinidase	$6,592	Not listed
Congenital Adrenal Hyperplasia	$10,000	Not listed
Congenital Hypothyroidism	$9,439	Not listed
Galactosemia	$9,439	Not listed
Homocystinurea	$122,515	Not listed
MCADD	$10,173	Not listed
Phenyl Ketonurea	$122,515	Not listed

61 Ibid.

62 Ibid.

Table 2.11 Life-time Cost of Various Sequeale of Inborn Errors of Metabolism – Carroll and Downs[63]

Type of Sequelae	Base Case Cost ($)	Threshold Values Obtained from Sensitivity Analysis
Blindness	$581,688	$180,000
Hospitalization before death	$27,809	Not listed
MCADD crisis	$308,315	Not listed
Deafness	$445,255	Not listed
Mild developmental delay	$44,192	$3,000
Moderate developmental delay	$77,079	Not listed
Severe developmental delay	$1,042,110	$450,000 to $685,000
Moderate cerebral palsy	$77,079	Not listed
Severe cerebral palsy	$216,848	$540,000

Table 2.12 Overall Cost-effectiveness of Various Screening Strategies Compared with No Screening – Carroll and Downs[64]

Strategy	Incremental cost	Incremental Effectiveness	C/E	Incremental C/E
MS/MS testing	-$43	0.004	0.72	Dominates
PKU test	-$35	0.00306	0.81	Dominates
BIOT test	-$13	0.0005	1.1	Dominates
CH test	-$5	0.00314	1.21	Dominates
HCY test	-$2	0.00019	1.24	Dominates
MSUD test	-$1	0.0002	1.26	Dominates
No test			1.26	
GAL test	$5	0.00005	1.32	$94,000
CAH test	$6	0.00028	1.34	$20,357

2.7.5 Feuchtbaum and Cunningham (2006)

This study is based on an economic evaluation of the annual costs of MS/MS screening of 540,000 infants born in California in one year. Table 2.13 describes the annualized costs incurred for MS/MS screening in California.

63 Ibid.
64 Ibid.

Table 2.13 Incremental Annualized Costs for MS/MS Screening in California Feuchtbaum and Cunningham[65]

Cost Category	**Cost Estimate (for 540,000 infants)**
Personnel and administration	$540,000
Equipment	$500,000
Supplies	$2,012,500
Laboratory contracts	$1,870,000
Follow-up	$742,000
Total	$5,664,500

The study estimated that the total cost of screening was $5.7 million. However, screening would save $7.2 million in treatment costs avoided. This would result in a net saving of $1.5 million. If the value of lives saved were included, the benefit-to-cost ratio for MS/MS screening was estimated at $9.32:1 ($11.67:1 under best case and $4.34:1 under worst case scenarios).[66]

Results of cost utility analysis of MS/MS screening are presented in Table 2.14.

65 Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. S280-286.

66 Ibid.

Table 2.14 Cost-utility Analysis of MS/MS Screening in California for 540,000 Infants - Feuchtbaum and Cunningham[67]

Estimates of marginal cost per QALY	Base case	Best Case	Worst Case
QALY saved	949	1,221	259
Cost per QALY (with $1 million life-time costs)	($1,628) dominant	($2,812) Dominant	$14,922
Cost per QALY (with 0.5 million life-time costs)	$2,389	$755	$19,129
Cost per QALY (with 1.5 million life-time costs)	($4,989) dominant	($5,797) Dominant	$11,401

2.7.6 Tran et al. (2007)

In a 2006 study based in Canada, Tran et al. studied the cost-effectiveness and clinical efficacy of newborn screening for MCADD using tandem mass spectrometry (MS/MS). The authors did not explicitly provide a break-down of all the costs included in their analysis. According to the study projections, for a hypothetical birth cohort of 330,803 infants (the birth rate in Canada for year 2003 – 2004), screening would cost C$934,923 (USD 719,890) over a 77-year horizon. Over the same period, the cost of *not* screening was estimated at C$450,521 (USD 346,901). Therefore, the incremental cost of screening is C$484,202 (USD 372,835). The study also estimated that screening would result in an additional 181 QALYs. The overall ICER for the base case was estimated at C$2,676/QALY (USD 2,060/QALY) gained.[68] Details of the economic

67 Ibid.

68 Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, Dooley K. Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin Biochem.* Feb 2007;40(3-4):235-241.

analysis presented in this study are shown in Table 2.15. The currency conversion rate for 2004 was 1C$ = 0.77 USD.[69]

Table 2.15 Results of Economic Analysis of Screening for MCADD Versus No Screening – Tran et al.[70]

Type of Analysis	**ICER (C$ per QALY)**
Base Case, Best and Worst Scenarios	
Base case	C$2,676/QALY
Best case	C$1,029/QALY
Worst case	C$11,463/QALY
One-way Sensitivity Analysis	
Screening cost C$(0.50 – 5.60)	Dominant (<0) to 6,963
Specificity (99.95 – 99.995)	C$3,095 to C$2,078/QALY
Cost of acute episode C$ (10,000 – 20,000)	C$2,585 to C$1,974/QALY
Incidence (1:20,000 – 1:14,286)	C$2,952 to C$1,647/QALY
Management cost C$(1,500 – 4,000)	C$2,150 to C$2,367/QALY
Cost of severe neurological impairment C$(100,000 – 250,000)	C$2,601 to C$1,960/QALY

2.7.7 Cipriano et al. (2007)

In a recent study Cipriano et al. examined the costs of expanding the newborn screening program in Ontario, Canada. In a decision analytic model that compared screening for individual disorders with screening the various disorders in groups of up to 21 conditions, costs and health benefits were compared for a hypothetical cohort of 130,000 newborns in Ontario in one year. The study included an account of start-up costs if the provincial newborn screening program were to be expanded. Other costs considered included estimates of per capita health care costs (stratified by different age groups), hospitalization costs, costs associated with additional healthcare services, costs

69 FX History: historical currency exchange rates. http://www.oanda.com/convert.fxhistory. Accessed September 15, 2007.

70 Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, Dooley K. Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin Biochem.* Feb 2007;40(3-4):235-241.

of diagnostics, costs of non-dietary as well as dietary treatments, costs of pharmaceutical treatments, costs of education and social services. It was assumed that an unscreened infant would show symptoms of the disorder which would then be diagnosed via clinical presentation. The cost of such a clinical diagnosis was estimated to be C$4,389 (2004 Canadian dollars).[71] This is equivalent to USD 3,380, based on a currency conversion rate of 1C$ = 0.77 USD.[72] All costs considered in the study are outlined in Table 2.16.

[71] Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

[72] {, #73}

Table 2.16 Base case Values and Costs of Screening Program, Healthcare, Hospitalization, Education and Social Services. (Costs in 2004 C$) Cipriano et al.[73]

Cost Category	Estimated Value
Cost of clinical diagnosis	C$4,389
Cost of Screening	
Annual equipment cost	C$490,380
Average staff expense per sample	C$0.85
Reagents and consumables per sample	C$13.46
Average Per Capita Healthcare Costs	
Average healthcare costs (<1 year)	C$5,211
Average healthcare costs (1-4 years)	C$800
Average healthcare costs (5-14 years)	C$693
Average healthcare costs (15-19 years)	C$1,089
Average healthcare costs (20-44 years)	C$1,825
Average healthcare costs (45-64years)	C$4,244
Average healthcare costs (65-79years)	C$7,736
Average healthcare costs (80+ years)	C$14,417
Hospitalizations	
Emergency room visit	C$1,167
Inpatient hospitalization, patient under 10 years	C$2,055
Inpatient hospitalization, patient over 10 years	C$1,765
Additional Health Care Services	
Initial call to schedule appointment (15-minute call with registered nurse)	C$7.03
Initial specialist consultation (all presumptive positives)	C$122.00
Subsequent pediatrician and specialist appointments (per appointment)	C$73.85
Registered dietician appointment (per 60-minute appointment)	C$75.96
Initial genetic counseling appointment (in the year of diagnosis)	C$238.20
Follow-up genetic counseling appointment (3 years after initial diagnosis)	C$100.90
Maintenance Diagnostics	
Quantitative amino acid diagnosis	C$108
Urine organic acids	C$108
Abdominal ultrasound	C$339
Non-dietary Treatments	
Hemodialysis – initial acute	C$1,045.15
Hemodialysis – chronic or repeat	C$537.40
Liver transplant	C$67,965.85

[73] Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

Kidney transplant	C$32,593.30

Table 2.16 Continued

Pharmaceutical Treatments (approximate annual costs)	
Arginine (660mg/kg/day)	C$41,063
Ascorbic acid (100mg/day)	C$30
Betaine (6g/day)	C$73
Carbamazepine (200mg/day)	C$90
Coalmine (1.5mg/day)	C$1,700
Cysteine (6g/day)	C$5,724
Glycine (375mg/kg/day)	C$685
L-carnitine (100mg/kg/day)	C$7,565
Medium chain triglycerideoil (120ml/day)	C$4,380
Metronidazole (250mg/day)	C$155
2-2nitro-4-triflouromethylbenzoyl (NTBC) (1mg/kg/day)	C$91,250
Pyridoxine (300mg/day)	C$82
Riboflavin (200mg/day)	C$58
Sodium phenyl butyrate (500mg/kg/day)	C$71,237
Thiamine (500mg/day)	C$3,980
Dietary Treatments	
Elemental formula (year 0)	C$4,000
Elemental formula (year 1-8)	C$5,000
Elemental formula (year 8-16)	C$6,000
Elemental formula (over 16 years)	C$5,000
Low protein foods (1-8 years)	C$2,000
Low protein foods (> 8 years)	C$3,500
Education and Social Services	
Standard education (5-18 years)	C$7,500
Additional classroom support	C$18,000
Advanced classroom support	C$27,000
Living in an assisted living facility	C$18,000
Living in an institutional facility	C$36,000
Social worker appointments (per 60 minute appointment)	C$76.98

Study results showed that in the base case, if the province of Ontario implemented MS/MS screening for PKU alone, it would cost an additional C$2.26 million (USD 1.74 million) annually. This strategy has an ICER of C$5,492,114 (USD 4,228,928) per life-year gained. Costs were estimated for incremental addition of one disorder at a time. It was estimated that screening for a group of disorders that included PKU and 14 other conditions would cost less than C$70,000 (USD 53,900) per life year gained. The incremental cost of including each of these disorders in the panel was less than C$100,000 (USD 77,000) per life year gained. However, the incremental cost spiked to C$309,400 (USD 238,238) per life year for the 15th disorder. It is likely that the sequence in which individual disorders were added to the screening panel was based on incidence and expected treatment costs. It was estimated that screening in groups (versus screening for each individual disorder) is a more cost-effective strategy (Table 2.17). However, not all disorders that can be detected via MS/MS are financially viable options for a newborn screening panel.[74]

[74] Ibid.

Table 2.17 Incremental Costs, Savings, Life-years Gained, and Cost-effectiveness of Adding Each Disease to a Screening Strategy in a Base Case Scenario Per Patient Screened. – Cipriano et al.[75]

Screening programs	**Diseases added**	**Increment-al cost of adding the disease in C$**	**Incremen-tal cost of the bundle in C$**	**Life-years gained by adding the disease in C$**	**Life-years gained for the bundle**	**ICER of adding the disease to the bundle in C$/LY**	**ICER of the bundle in C$/LY**
PKU	Phenylketonuria	17.41	17.41	0.0317	0.0317	5,492,114	5,492,114
PKU+1	Methylmalonic academia	1.03	18.44	0.754	0.796	13,482	231,746
PKU+2	HMG-CoA lyase deficiency	1.23	19.67	0.884	1.68	13,914	117,104
PKU+3	Maple Syrup Urine Disease	0.87	20.54	0.564	2.24	15,426	91,545
PKU+4	Propionic acidemia	1.74	22.28	0.624	2.87	27,885	77,693
PKU+5	VLCADD	1.60	23.88	0.432	3.30	37,037	72,370
PKU+6	Carnitine transported defect	1.52	25.40	0.359	3.66	42,340	69,424
PKU+7	Glutaric acidemia type I	3.24	28.64	0.674	4.33	48,071	66,102
PKU+8	Isovaleric acidemia	0.75	29.39	0.125	4.46	60,000	65,931
PKU+9	MCADD	6.06	35.45	0.965	5.42	62,798	65,373
PKU+10	3-methylcrotonyl-CoA carboxylase deficiency	6.30	41.75	0.924	6.35	68,182	65,782
PKU+11	LCADD	0.63	43.38	0.188	6.53	86,702	66,384
PKU+12	Carnitine palmitoyl transferase I	1.55	44.93	0.167	6.70	92,814	67,043

[75] Ibid.

	deficiency						
PKU+13	Carnitine palmitoyl transferase II deficiency	1.65	46.58	0.176	6.88	93,754	67,726
PKU+14	Carnitine translocase deficiency	1.52	48.10	0.160	7.04	95,000	68,346
PKU+15	Tyrosenemia type I	14.14	62.24	0.457	7.49	309,409	83,045
PKU+16	Homocytineuria	2.07	64.31	0.0625	7.56	331,200	85,098
PKU+17	Arginosuccinic aciduria	44.52	108.83	0.309	7.87	1,440,777	138,351
PKU+18	Citrillinemia	42.44	151.27	0.242	8.11	1,753,719	186,564
PKU+19	Arginemia	29.38	180.65	0.120	8.23	2,448,333	219,550
PKU+20	Glutaric acidemia type II	0.72	181.37	.00134	8.23	5,373,134	220,389

VLCADD= Very long chain acyl-CoA dehydrogenase deficiency
LCADD =Long chain hydroxyl acyl-CoA dehydrogenase deficiency
MCADD=Medium chain acyl-CoA dehydrogenase deficiency

2.8 SUMMARY OF STUDIES

The studies conducted so far support the cost-effectiveness of newborn screening with MS/MS. There is an agreement that simply replacing the Guthrie test for PKU with MS/MS is not cost-effective. However, if multiple disorders are included in the screening panel, the incremental cost is not very high. Therefore, in the long run, it is possible to offset or reduce the costs incurred in screening. However, there is little uniformity in terms of the disorders included, the likelihood of some of the adverse outcomes, the costs included and the range of these costs. Inclusion or exclusion of certain disorders in an economic analysis can lead to different cost and outcome estimates. Study results would also differ if indirect costs such as productivity loss are included in the estimate. There are also variations in the dollar value of some treatment costs as well as the likelihood of some of the sequelae. All of these variations can lead to different results. Despite these differences, most study results are below the commonly used threshold of $50,000/QALY.

2.9 STUDY RATIONALE AND OBJECTIVES

From the above review of literature, it becomes clear that newborn screening is a multifaceted topic with clinical, ethical, legal and economic implications. All of these aspects need to be researched, especially in the light of recent expansions in the newborn screening panels being offered by state health services across the country. Among other factors, the ability to test for multiple disorders is closely tied with the need for additional resources for confirmatory testing, long-term treatment and disease management. Timely diagnosis and treatment are likely to result in reduced morbidity and mortality associated with these rare but serious disorders. After the latest expansion in the Texas newborn screening panel, a systematic health economic analysis is warranted to understand the

long-term implications (in terms of costs and patient outcomes) of this important policy decision. This study is intended to estimate the cost-effectiveness of expanded newborn screening in Texas and to answer related questions. The objectives of this study are:

1. To describe the demographic characteristics of the infant population served by the Texas newborn screening program;
2. To describe the incidence of various disorders since the expansion of the newborn screening program in Texas and compare the incidence of each disorder with the estimates published in the literature;
3. To estimate the average input cost to the state for providing expanded screening and confirmatory testing for positive screens;
4. To estimate the average costs of follow-up and treatment for infants who test positive (by disorder);
5. To estimate the average QALYs for infants who test positive (by disorder) and draw a comparison between expanded and pre-expansion strategies; and
6. To estimate whether the expanded newborn screening program in Texas is cost-effective.

2.10 STUDY HYPOTHESES

This section provides details about the hypotheses that were developed for the above study objectives. Of the six objectives, hypotheses were developed for objectives 4, 5 and 6.

2.10.1 Hypotheses for Objective One

The first objective was to describe the demographic characteristics of the infant population served by the Texas newborn screening program. Data is available about the

demographic characteristics of Texas births for 2005. No hypothesis is needed for this objective.

2.10.2 Hypotheses for Objective Two

The incidence of the newly added disorders in the Texas newborn screening panel has only been recorded since the program expansion in 2007. This information was obtained from the Texas Department of State Health Services (DSHS). No hypothesis is needed for this objective.

2.10.3 Hypotheses for Objective Three

Average costs associated with expanded newborn screening and confirmatory testing were obtained from DSHS and Institute of Metabolic Disease at Baylor Research Institute. No hypothesis is needed for this objective.

2.10.4 Hypotheses for Objective Four

Average direct medical costs associated with follow-up and treatment such as cost of special diet and medications, inpatient and outpatient expenses were compared between the expanded and pre-expansion screening strategies.

H4.1 $\text{Cost}_{\text{ASA\_CIT expanded screening}} \geq \text{Cost}_{\text{ASA\_CIT pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Arginosuccinic aciduria (ASA) and Citrullinemia (CIT) for the expanded screening strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.2 $\text{Cost}_{\text{HCY expanded screening}} \geq \text{Cost}_{\text{HCY pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Homocystinuria (HCY) for the expanded screening strategy are greater

than or equal to the average direct medical costs for the pre-expansion strategy.

H4.3 $\text{Cost}_{\text{TYR expanded screening}} \geq \text{Cost}_{\text{TYR pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Tyrosinemia (TYR) for the expanded screening strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.4 $\text{Cost}_{\text{MCADD expanded screening}} \geq \text{Cost}_{\text{MCADD pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) for the expanded screening strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.5 $\text{Cost}_{\text{GA I expanded screening}} \geq \text{Cost}_{\text{GA I pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Glutaric Acidemia type I (GA I) for the expanded screening strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.6 $\text{Cost}_{\text{MSUD expanded screening}} \geq \text{Cost}_{\text{MSUD pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Maple Syrup Urine Disease (MSUD) for the expanded screening strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.7 $\text{Cost}_{\text{COAD expanded screening}} \geq \text{Cost}_{\text{COAD pre-expansion screening}}$

Average direct medical costs associated with follow-up and treatment of Classical Organic Acid Disorders (COAD) for the expanded screening

strategy are greater than or equal to the average direct medical costs for the pre-expansion strategy.

H4.8 $\text{Cost}_{\text{OVERALL expanded screening}} \geq \text{Cost}_{\text{OVERALL pre-expansion screening}}$

Overall direct medical costs associated expanded screening strategy are greater than or equal to the overall direct medical costs for the pre-expansion strategy.

2.10.5 Hypotheses for Objective Five

The Quality Adjusted Life Years (QALYs) were compared between the expanded and pre-expansion screening strategies.

H5.1 $\text{QALYs}_{\text{ASA\_CIT expanded screening}} \geq \text{QALYs}_{\text{ASA\_CIT pre-expansion screening}}$

The average QALYs for Arginosuccinic aciduria (ASA) and Citrullinemia (CIT) patients diagnosed via expanded screening are greater than or equal to those for ASA and CIT patients diagnosed via pre-expansion screening.

H5.2 $\text{QALYs}_{\text{HCY expanded screening}} \geq \text{QALYs}_{\text{HCY pre-expansion screening}}$

The average QALYs for Homocystinuria (HCY) patients diagnosed via expanded screening are greater than or equal to those for HCY patients diagnosed via clinical symptoms pre-expansion screening.

H5.3 $\text{QALYs}_{\text{TYR expanded screening}} \geq \text{QALYs}_{\text{TYR pre-expansion screening}}$

The average QALYs for Tyrosinemia (TYR) patients diagnosed via expanded screening are greater than or equal to those for TYR patients diagnosed via pre-expansion screening.

H5.4 $\text{QALYs}_{\text{MCADD expanded screening}} \geq \text{QALYs}_{\text{MCADD pre-expansion screening}}$

The average QALYs for Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) patients diagnosed via expanded screening are

greater than or equal to those for MCADD patients diagnosed via pre-expansion screening.

H5.5 $QALYs_{\text{GA I expanded screening}} \geq QALYs_{\text{GA I pre-expansion screening}}$

The average QALYs for Glutaric Acidemia (GA I) patients diagnosed via expanded screening are greater than or equal to those for GA I patients diagnosed via pre-expansion screening.

H5.6 $QALYs_{\text{MSUD expanded screening}} \geq QALYs_{\text{MSUD pre-expansion screening}}$

The average QALYs for MSUD patients diagnosed via screening are greater than or equal to those for MSUD patients diagnosed via pre-expansion screening.

H5.7 $QALYs_{\text{COAD expanded screening}} \geq QALYs_{\text{COAD pre-expansion screening}}$

The average QALYs for Classical Organic Acid Disorders (COAD) patients diagnosed via screening are greater than or equal to those for COAD patients diagnosed via pre-expansion screening.

H5.8 $QALYs_{\text{OVERALL expanded screening}} \geq QALYs_{\text{OVERALL pre-expansion screening}}$

The overall QALYs for patients diagnosed via screening are greater than or equal to those for patients diagnosed via pre-expansion screening.

2.10.6 Hypotheses for Objective Six

A ceiling cost ratio (Rc) is often used as a threshold of cost-effectiveness value. The Rc for this study is equivalent to the willingness to pay (WTP) for an additional quality adjusted life year (QALY) in a child affected with one of the inborn errors of metabolism. In previous studies, a WTP of $50,000/QALY has been used which is also consistent with the convention in the Health Economics literature in general. The

Incremental Cost-effectiveness Ratio (ICER) for expanded screening strategy was compared with the pre-expansion screening strategy.

H6.1 $ICER_{ASA\_CIT\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for ASA and CIT is less than or equal to the Rc of $50,000/QALY

H6.2 $ICER_{HCY\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for HCY is less than or equal to the Rc of $50,000/QALY

H6.3 $ICER_{TYR\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for TYR is less than or equal to the Rc of $50,000/QALY

H6.4 $ICER_{MCADD\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for MCADD is less than or equal to the Rc of $50,000/QALY

H6.5 $ICER_{GA\ I\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for GA I is less than or equal to the Rc of $50,000/QALY

H6.6 $ICER_{MSUD\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for MSUD is less than or equal to the Rc of $50,000/QALY

H6.7 $ICER_{COAD\ expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The ICER of expanded versus pre-expansion screening for COAD is less than or equal to the Rc of $50,000/QALY

H6.8 Overall $ICER_{expanded\ screening\ versus\ pre\text{-}expansion\ screening} \leq Rc$

The overall ICER of expanded versus pre-expansion screening for is less than or equal to the Rc of $50,000/QALY

Chapter Three - Methodology

This chapter provides a detailed account of the study methodology. It consists of six sections. Section one includes a description of the sources of data that were used in this study. Section two is comprised of a brief discussion of the study population and the inclusion and exclusion criteria. Section three covers the theoretical basis of economic evaluation in healthcare and includes a section on the theory behind cost-effectiveness analysis. Section four discusses the general concepts of decision analysis and a detailed description of the vital elements of Markov modeling. Section five contains an overview of categories of costs used in the cost-effectiveness analysis. Section six contains tabular representations of the estimated costs, probability values and utility values associated with each of the disorders included in the cost-effectiveness analysis. The structure of the Markov model that was used for the cost-effectiveness analysis is also included in this section.

3.1 Sources of Data

As outlined in the review of literature, newborn screening has been studied by various researchers. Decision analysis and modeling techniques using estimates from existing literature have been frequently used in these studies. For the purpose of this study, data were required for incidence of disorders, cost of screening, costs of various sequelae, and probabilities of various sequelae. Information on these variables was needed for each of the disorders included in the study. The disorders included in this study (defined as post-expansion screening) were: Arginosuccinic Acidemia (ASA); Citrullinemia (CIT); Homocystinuria (HCY); Maple Syrup Urine Disease (MSUD); Glutaric Acidemia Type I (GA I); Medium Chain Acyl CoA Dehydrogenase Disorder (MCADD) and other Fatty Acid Disorders; Tyrosinemia (TYR); and Classical organic

Acid Disorders (COAD) [including MMA (Methylmalonic academia), PA (Propionic Acidemia) and IVA (Isovaleric Acidemia)]. Since ASA and CIT were combined into one disorder category because of very similar clinical outcomes, the Markov model included seven sub-trees representing each of the categories mentioned above. Another sub-tree was used for representing the healthy child.

3.1.1 Incidence

Incidence data was obtained from the Texas DSHS (Department of State Health Services) case management division. This division maintains an updated record of all newborns that test positive for any of the disorders screened by the newborn screening program.

3.1.2 Costs

Since this study was conducted from a payer's perspective, only direct medical costs were included. These costs were obtained from DSHS, Baylor Institute of Metabolic Disease and from the literature as described below.

3.1.2.1 Cost of Screening

The State of Texas performs two screens on every newborn at the ages of 24-48 hours and 7-14 days respectively. Blood samples from infants who test positive after the second screen need to be sent for confirmatory testing. The total cost of screening includes the cost of the first and second screens and the cost of confirmatory testing. Equipment costs were not included because the state public health laboratory rents the equipment from a company where it is required to pay only for the recurrent reagent costs. The cost of reagent is reflected in the cost of screening.

3.1.2.2 Cost of Sequelae

Within the scope of the current study, it seems logical to use actual cost data from Texas Medicaid to estimate the incidence of various disorders and for assessing the costs incurred for the treatment of positive cases. However, after consulting with some of the experts in newborn screening, it became clear that estimating the cost of sequelae from Medicaid data may not be the best approach. Experts also believe that for most disorders, the sequelae are too ambiguous to be accurately reflected in a single ICD-9 code. Further, the diagnosis may not be stratified by severity of the underlying condition (such as mild, moderate or severe). For example, mental retardation can be a sequela for many of the metabolic disorders being studied. A child suffering from mental retardation may need many services in addition to physician visits. Medicaid data may not be the single best source for estimating all of these costs. Further, children showing only mild symptoms of mental retardation may not be classified as mentally retarded and may utilize far fewer services than children with more severe forms of the condition. Therefore, although this study will specifically address the perspective of the State of Texas, cost data were estimated based on published studies and expert opinion.

3.1.3 Probabilities of Sequeale

It is important to have accurate estimates of the likelihood of various sequeale for conducting a rational cost-effectiveness analysis. These probabilities were obtained from the literature and expert opinion.

3.2 TARGET POPULATION

The target population for this study is all infants born in the State of Texas since the expansion of the newborn screening program in 2007. Data for the year [2007] were used.

3.2.1 Inclusion and Exclusion Criteria

The Markov model for cost-effectiveness analysis included a hypothetical cohort of infants born in Texas in 2007. Published estimates of incidence data were used to assign probabilities for the occurrence of various disorders. Actual incidence data (obtained from DSHS) was then compared with the expected incidence. False positive rates were also obtained from historical data from DSHS. False positive rates were necessary for allocating costs of confirmatory testing for all presumptive positive cases. For other cost estimates, studies published from1998-2008 were reviewed.

3.3 THEORETICAL BASIS OF ECONOMIC EVALUATION OF HEALTH CARE

Welfare analysis forms the core of most economic evaluations. In social welfare, an individual is the basic unit of analysis and aggregates of individual economic activity constitute social welfare. Each individual tries to maximize his/her utility where utility is defined as the satisfaction derived from a good or service. Utilities of all individuals taken together constitute social welfare. Welfare analysis seeks to evaluate the economic impact of the various ways of allocating the available resources. The goal of welfare analysis is to answer the following questions:[76]

Is a certain resource allocation efficient?

Who are the gainers and losers from this allocation? What is the extent of their gains or losses?

3.3.1 Paretian Welfare Economics

Paretian welfare economics has two central concepts: Pareto improvement and Pareto efficiency. A Pareto improvement is said to have occurred if a certain reallocation of resources leads to an increase in utilities of at least one individual. If there are some

[76] Drummond M, Alistair M, eds. *Economic Evaluation in Healthcare*. Oxford: Oxford University Press; 2001.

losers and some gainers, the outcomes of the reallocation process are said to be Pareto non-comparable because of the non-comparable nature of individual utilities. Figure 3.1 illustrates a hypothetical plot of the utilities of two individuals(U1 and U2). If e is the starting point, then a reallocation that leads to y can be considered a Pareto improvement. Conversely, a change from e to w will be considered Pareto deterioration. On the other hand, movement from e to x or e to z can neither be called an improvement, nor deterioration. An extension of this idea can be that all points in quadrant B are Pareto superior to e while all points in quadrant C are Pareto inferior with respect to e. However, in quadrants A and D, one individual's gain is another's loss. Therefore, all states in these two quadrants can be termed Pareto non-comparable.[77]

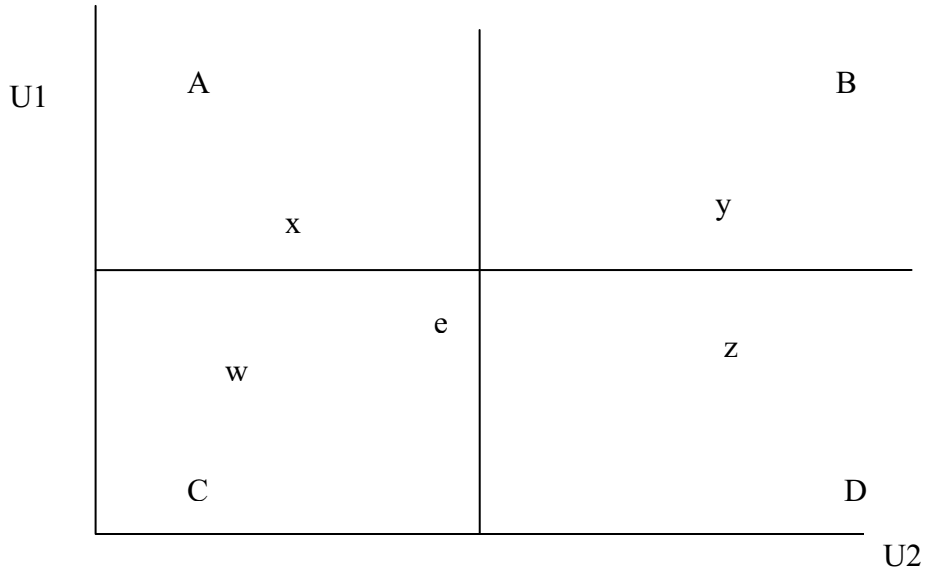

Figure 3.1 Pareto Comparable and Pareto Non-comparable States

[77] Ibid.

3.4 WILLINGNESS TO PAY

Willingness to pay (WTP) or compensating variation (CV) is a way to establish preferences among options that are Pareto non-comparable. WTP may be defined as the amount of money that an individual is willing to give up in order to attain a certain improvement in his/her health status. According to this approach, monetary values are placed on Pareto non-comparable choices. An aggregate of these monetary values can be translated into gain or loss in consumer welfare. Therefore, with CV, it would be possible to decide whether or not it was better for an individual to move from state e to x or state e to z (Fig. 3.1). However, this generalization does suffer from the limitation that the value of $1 should be held constant for every individual.

This reallocation of resources where monetary values are placed on different options is central to many health economic analyses such as the cost-benefit analysis (CBA). Health economic analyses frequently use Quality Adjusted Life Years (QALYs) as a comparator across individuals. As mentioned in Chapter 2, QALYs represent the quantity and the quality of life in a single unit. For example, each year of life lived in perfect health is assigned a value of 1.0 while death is assigned a value of 0. A disease state may be represented on this continuum by a value that is greater than 0 but less than 1.0.[78]

3.4.3 Cost-effectiveness Analysis

If cost of treatment 'a' is C_a, cost of treatment b is C_b, effect of treatment a is E_a, and that of treatment b is E_b then cost-effectiveness can be represented as a ratio called the Incremental Cost Effectiveness Ratio (ICER)[79]:

---

78 Bootman JL, Townsend RJ, McGhan WF. *Principles of Pharmacoeconomics*. Third ed. Cincinnati, OH: Harvey Whitney Books Company; 2005.

79 Drummond M, Alistair M, eds. *Economic Evaluation in Healthcare*. Oxford: Oxford University Press; 2001.

$$ICER = \frac{C_a - C_b}{E_a - E_b}$$

This equation can be extrapolated to a population level where the cost of treatment A is μCA and the cost of treatment B is μCB. Similarly expected population values of effects of treatments A and B can be represented by μEA and μEB. Then various outcomes of incremental costs and effects may be summarized in the following four states[80]:

1. μCA - μCB < 0; μEA - μEB > 0; an outcome where treatment A is both less expensive and more effective than treatment B (dominant).
2. μCA - μCB > 0; μEA - μEB < 0; an outcome where treatment B is both less expensive and more effective that treatment A (dominant).
3. μCA - μCB > 0; μEA - μEB > 0; an outcome that represents a trade-off such that treatment A is both more expensive and more effective than treatment B.
4. μCA - μCB < 0; μEA - μEB < 0; an outcome that represents another trade-off situation where treatment B is both more expensive and more effective than treatment A.

If the outcomes of two competing alternatives are to be compared in non-monetary terms (such as health benefits), then QALYs are the preferred choice. Decision makers seek strategies that maximize QALYs at the lowest cost.

3.5 DECISION ANALYSIS

Decision analysis is a formal methodology of analyzing the alternatives available to a decision maker. As shown in fig. 3.2, each alternative is represented by a "branch"

[80] Ibid.

of a "tree." Uncertainty associated with each alternative is represented by a probability value. The final outcome of each alternative is calculated as a weighted measure of its value. The weight is represented by the respective probability of that outcome. Decision analysis is based on a set of basic rules[81]:

a) The tree flows from left to right where the earliest events are listed at the extreme left and successive events are listed to the right.
b) Events in the tree are represented by various nodes. Decision nodes (showing the available choices) are represented as squares; chance nodes (showing the likely outcomes) are represented by circles; and terminal nodes (showing the final outcome) are represented by triangles.
c) Branches originating from the decision node should represent all the choices and each of those choices should be mutually exclusive.
d) Branches originating from the chance node should represent the likely outcomes. Each of these outcomes should be mutually exclusive such that their probabilities sum to 1.0.
e) Terminal nodes should represent the net "pay off" of various alternatives shown in the model.

[81] Sonnenberg M, Beck J. Markov models in medical decision making. *Med Decis Making.* 1993;13:322-338.

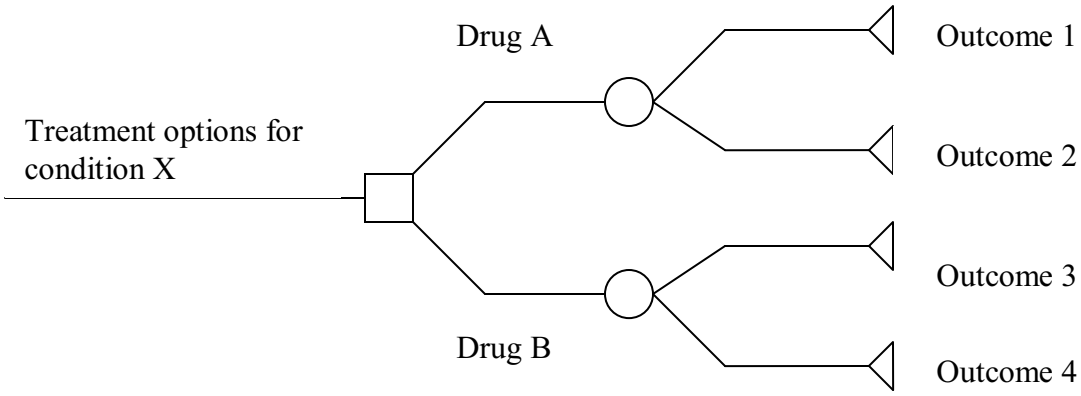

Figure 3.2 Depiction of a Basic Decision Analysis Tree

3.5.1 Basics of Markov Modeling

Markov models are a popular method of estimating disease prognosis and life expectancy. In its initial usage, researchers used matrix algebra to develop a fundamental model that estimated the length of time a patient might spend in a particular health state. Since then, Markov models have evolved substantially. Most present day researchers use sophisticated decision analytic software to construct and evaluate Markov models. The following paragraphs discuss some of the key concepts in Markov modeling.[82]

A Markov model is based on the assumption that a patient can be in one and only one health state at a given time. This is called a Markov state. Each Markov state has a specific utility value. The total time-frame included in a Markov analysis is divided into equal intervals. Each interval represents a Markov cycle. As one Markov cycle leads into the next cycle, it is possible for a patient to move to another health state or continue to stay in the same health state. The utility attributed to a specific health state is called the Incremental Utility of that health state. The Expected Utility of the entire Markov process is an aggregate of incremental utilities of each of the health states multiplied by the length of time spent in that state.[83]

$$\text{Expected Utility} = \sum_{s=1}^{n} t_s \text{ X } U_s$$

Where ts = time spent in a health state and Us = Utility of that health state

For example, if a patient spends 3.5 years in the "Well" state and 2 years in the "Disabled" state and then enters the "Dead" state, the expected utility would be:

$$\text{Expected Utility} = (3.5 \text{ X } 1.0) + (2 \text{ X } 0.6) = 4.7 \text{ QALY}$$

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82 Ibid.

83 Ibid.

Utility of "Well" state = 1.0

Utility of "Disabled" state = 0.6

This analysis can also be further expanded to include financial cost of being in each state for a given length of time.

A transition probability is the likelihood that a patient may move from one health state to another. Theoretically, a Markov process with "n" states may be represented by n^2 transition probabilities. However, in practice, the probability of "disallowed" transitions is zero. For example, the probability that a patient will transition from "Dead" to "Well" or from "Dead" to "Disabled" is zero. Each Markov process includes at least one permanent state; one from which a patient cannot transition into another state. Such a Markov state is termed as an Absorbing state. At the end of the Markov process, all the patients will end up in the absorbing state. "Death" is an example of an absorbing state. In a Markov process, certain states may be such that a patient can stay in them for only a limited period of time (at the most one cycle). Eventually the patient has to transition to another state. These states are known as Temporary states and are frequently used to assign specific utility values and costs associated with a health state. For example, if an infant suffers a metabolic crisis, he/she may transition to "Disabled" or "Dead" state. It is not possible to stay in the "Metabolic Crisis" state for a very long time. However, the use of this state may enable the researcher to allocate costs associated with such an event. Further, the probability of death for an infant who has suffered a metabolic crisis event may be different from the one without it. Therefore, transition states help in making a Markov model more accurate and realistic. Tunnel states are a series of temporary states that may be followed only in a certain sequence. Just like the individual transition states,

tunnel states can also facilitate the assignment of transition probabilities and costs for special events. In this case, however, the event may last longer than one Markov cycle.[84]

3.6 COSTS INCLUDED

The study included all direct medical costs incurred during the screening process as well during follow-up and treatment of positive cases. Direct non-medical costs such as transportation and indirect or productivity costs such as wages lost by caregivers were not included because the study was conducted from a payer's perspective. A base discount rate of 3% was used in all the calculations.

3.6.1 Direct Medical Costs

Direct medical costs related to newborn screening can vary depending on the underlying disease state and the severity of sequelae experienced by the patient. For the purpose of this study the following cast categories were considered:

1. Cost of screening
2. Cost of confirmatory testing
3. Cost of false positive results
4. Cost of disease management such as cost of special diet, cost of medications, cost of emergency room visits, cost of inpatient stay etc.
5. Cost of specific sequelae such as cost of mental retardation, cost of neurological damage, cost of developmental delay, cost of lens dislocation, cost of spinal osteoporosis, cost of chronic renal failure, cost of liver transplant etc.

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[84] Ibid.

3.7 MODEL INPUTS

The following tables (3.1 - 3.3) describe the model inputs for estimated costs, probability values and utility values. Variable names, their short description, their base value, their high and low values (for sensitivity analysis), and source of data are included. Ranges of variables were based on a mix of clinical and economic information. For probability estimates, overall life-time values are presented. Details of yearly estimates of probability values (wherever applicable), of clinical outcomes in each disorder category are presented in Appendix H.

Table 3.1 Cost Estimates

Variable Name	Description	Estimated Average Cost	Lower Estimate of Cost	Higher Estimate of Cost	Reference
C_carnitine	Yearly cost of Carnitine supplements for MCADD	$5,000	$4,000	$6,000	Insinga, Schoen
C_CRF	Yearly cost of chronic renal failure	$3,600	$3,200	$4,000	Smith [85]Estimate
C_DD	Yearly cost of developmental delay	$500.	$400	$600	Honeycutt[86]
C_Diet	Yearly cost of special diet for metabolic disorders	$5,000	$4,000	$6,000	Cipriano[87]
C_ER_MCADD_Scr	Yearly cost of emergency room visits for MCADD patients	$500	$400	$600	Hsu[88], Haas[89],Wilcken[90]
C_Expanded	One time cost of expanded newborn screen	$59			Texas Department of State Health Services Data
C_InPt_MCADD_Scr	Yearly cost of inpatient stay for MCADD patients	$2,500	$2,000	$3,000	Hsu[91], Haas[92], Wilcken[93]

85 Smith DH, Gullion CM, Nichols G, Keith DS, Brown JB. Cost of medical care for chronic kidney disease and comorbidity among enrollees in a large HMO population. *J Am Soc Nephrol.* May 2004;15(5):1300-1306.

86 Honeycutt A, Grosse S, Dunlap L, et al. Economic costs of mental retardation, cerebral palsy, hearing loss, and vision impairment. *Research in Social Science and Disability.* 2003;3:207-228.

87 Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

88 Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

89 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

90 Wilcken B, Haas M, Joy P, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet.* Jan 6 2007;369(9555):37-42.

Variable Name	Description	Estimated Average Cost	Lower Estimate of Cost	Higher Estimate of Cost	Reference
C_LD	One-time cost of lens dislocation	$2,300	2,000	2,500	Busbee[94]
C_LT	One-time cost of liver transplant	$200,000	150,000	250,000	US Department of Veteran Affairs[95]
C_Med_ASA_CIT	Yearly cost of ASA and CIT medications	$40,000	$36,000	$44,000	Cipriano[96]
C_Med_HCY	Yearly cost of medications for homocystinuria	$5,000	$4,000	$6,000	Cipriano[97]
C_Med_COAD	Yearly cost of medications for classical organic acid disorders	$1,700	$1,500	$2,000	Cipriano[98]
C_Med_Tyr	Yearly cost of medication to prevent liver damage in tyrosinemia	$12,000	$10,000	$14,000	Cipriano
C_MR	Annual cost mental retardation	$4,200	$3,000	$5,000	Honeycutt[99]

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91 Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

92 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

93 Wilcken B, Haas M, Joy P, et al. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet.* Jan 6 2007;369(9555):37-42.

94 Busbee BG, Brown MM, Brown GC, Sharma S. Incremental cost-effectiveness of initial cataract surgery. *Ophthalmology.* Mar 2002;109(3):606-612; discussion 612-603.

95 How much does a liver transplant cost? *National Hepatitis C Program* [http://www.hepatitis.va.gov/vahep?page=trans-01-07. Accessed September 24, 2008.

96 Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

97 Ibid.

98 Ibid.

99 Honeycutt A, Grosse S, Dunlap L, et al. Economic costs of mental retardation, cerebral palsy, hearing loss, and vision impairment. *Research in Social Science and Disability.* 2003;3:207-228.

C_ND	Annual cost neurological disorders	$2,900	$2,000	$3,800	Honeycutt[100]
Variable Name	**Description**	**Estimated Average Cost**	**Lower Estimate of Cost**	**Higher Estimate of Cost**	**Reference**
C_Pre_Expansion	One time of cost of screening before expansion	$39			Department of State Health Services Data
C_SO	Yearly cost of spinal osteoporosis	$400	$300	$500	Yeh[101]

100 Ibid.

101 Yeh J-Y. *Cost-effectiveness analyses of anti-resorptive agents for management of glucocorticoid-induced osteoporosis and fractures: Empirical estimates from the 1996--2004 MEPS data and longitudinal projection from Markov modeling* [Ph.D.]. United States -- Texas, The University of Texas at Austin; 2007.

Table 3.2 Probability Estimates

Variable Name	Description	Base Case Estimate of Probability	Range	Reference
P_ASA_and_CIT	Probability of being true positive for ASA and CIT	0.00002		Department of State Health Services Data
P_COAD	Probability of being true positive for classical organic acid disorders	0.00002		Department of State Health Services Data
P_CRF_COAD_NoScr	Probability of chronic renal failure due to classical organic acid disorders without screening	0.412	0.370 - 0.453	Dionisi-Vici[102], Expert opinion[103]
P_CRF_COAD_WithScr	Probability of chronic renal failure due to classical organic acid disorders with screening	0.050	0.045 – 0.055	Dionisi-Vici[104], Expert opinion[105]
P_DD_MSUD_NoScr	Probability of developmental delay due to MSUD without screening	0.060	0.045 – 0.075	Morton[106]
P_DD_MSUD_WithScr	Probability of developmental delay due to MSUD with screening	0.022	0.018 – 0.026	Morton[107]
P_Death_GAI_NoScr	Probability of death due to GA I without screening	0.320	0.288 – 0.352	Strauss[108],

102 Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

103 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

104 Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

105 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

106 Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* Jun 2002;109(6):999-1008.

107 Ibid.

				Kyllerman[109], Expert Opinion[110]
P_Death_GAI_WithScr	Probability of death due to GA I with screening	0.050	0.045 – 0.056	Strauss[111], Kyllerman[112], Expert Opinion[113]
P_Die_ASA_CIT_NoScr	Probability of death due to ASA and CIT without screening	0.805	0.644 – 0.966	Expert opinion[114]
P_Die_ASA_CIT_WithScr	Probability of death due to ASA and CIT with screening	0.605	0.484 – 0.726	Expert opinion[115]
P_Die_COAD_NoScr	Probability of death due to classical organic acid disorders without screening	0.505	0.454 – 0.555	Dionisi-Vici[116], Expert opinion[117]
P_Die_COAD_WithScr	Probability of death due to classical organic acid disorders with screening	0.110	0.099 – 0.121	Dionisi-Vici[118], Expert opinion[119]

[108] Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: natural history of 77 patients. *Am J Med Genet C Semin Med Genet.* Aug 15 2003;121C(1):38-52.

[109] Kyllerman M, Skjeldal OH, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations. *Mov Disord.* Jan 1994;9(1):22-30.

[110] Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

[111] Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: natural history of 77 patients. *Am J Med Genet C Semin Med Genet.* Aug 15 2003;121C(1):38-52.

[112] Kyllerman M, Skjeldal OH, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations. *Mov Disord.* Jan 1994;9(1):22-30.

[113] Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

[114] Ibid.

[115] Ibid.

[116] Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

[117] Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

[118] Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

[119] Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

P_Die_HCY_NoScr	Probability of death due to HCY without screening	0.140	0.042 – 0.237	Mudd[120], Scriver[121]
P_Die_HCY_WithScr	Probability of death due to HCY with screening	0.100	0 – 0.200	Mudd[122], Scriver[123]
P_Die_MCADD_NoScr	Probability of death due to MCADD without screening	0.250	0.225 – 0.275	Hsu[124], Haas[125], Grosse[126]
P_Die_MCADD_WithScr	Probability of death due to MCADD with screening	0.042	0.037 – 0.045	Hsu[127], Haas[128], Grosse[129]
P_Die_MSUD_NoScr	Probability of death due to MSUD without screening	0.900	0.800 – 1.00	Morton[130]
P_Die_MSUD_WithScr	Probability of death due to MSUD with screening	0.060	0.045 – 0.075	Morton[131]

120 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

121 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

122 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

123 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

124 Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

125 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

126 Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

127 Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

128 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

129 Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

130 Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* Jun 2002;109(6):999-1008.

131 Ibid.

P_DX_TYR_NoScr	Probability of clinical diagnosis of tyrosinemia	1		Holme[132]
P_FP_Exp	Probability of false positive in expanded screen	0.020	0.018 - 0.022	Department of State Health Services Data
P_FP_UnExp	Probability of false positives in unexpanded screening	0.0175	0.010 - 0.019	Department of State Health Services Data
P_GAI	Probability of being true positive for GA I	0.00005		Department of State Health Services Data
P_HCY	Probability of being true positive for HCY	0.000005		Department of State Health Services Data
P_LD_HCY_NoScr	Probability of lens dislocation due to HCY without screening	0.708	0.567 – 0.850	Mudd[133], Scriver[134]
P_LD_HCY_WithScr	Probability of lens dislocation due to HCY with screening	0.050	0 – 0.100	Mudd[135], Scriver[136]
P_LD_TYR_NoScr	Probability of liver damage due to TYR without screening	0.120	0.090 – 0.150	Holme[137]
P_MCADD	Probability of being true positive for MCADD and other fatty acid disorders	0.0001		Department of State Health Services Data
P_MR_ASA_CIT_NoScr	Probability of MR due to ASA and CIT without	0.200	0.160 -0.240	Expert opinion[138]

132 Ibid.

133 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

134 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

135 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

136 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

137 Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inherit Metab Dis.* Aug 1998;21(5):507-517.

138 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

	screen			
P_MR_ASA_CIT_WithScr	Probability of MR due to ASA and CIT with screen	0.200	0.160 -0.240	Expert opinion[139]
P_MR_HCY_NoScr	Probability of mental retardation due to HCY without screening	0.892	0.793 – 0.991	Mudd[140], Scriver[141]
P_MR_HCY_WithScr	Probability of mental retardation due to HCY with screening	0.090	0 - 0.181	Mudd[142], Scriver[143]
P_MSUD	Probability of MSUD	0.000005		Department of State Health Services Data
P_ND_COAD_NoScr	Probability of neurological damage due to classical organic acid disorders without screening	0.733	0.659 – 0.806	Dionisi-Vici[144], Expert opinion[145]
P_ND_COAD_WithScr	Probability of neurological damage due to classical organic acid disorders with screening	0.273	0.245 – 0.300	Dionisi-Vici[146], Expert opinion[147]
P_ND_GAI_NoScr	Probability of neurological damage due to GA I without screening	0.906	0.724– 0.996	Strauss[148], Keyllerman[149], Expert Opinion[150]

139 Ibid.

140 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

141 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

142 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

143 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

144 Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

145 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

146 Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

147 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

148

P_ND_GAI_WithScr	Probability of neurological damage due to GA I with screening	0.350	0.315 – 0.386	Strauss[151], Kyllerman[152], Expert Opinion[153]
P_ND_MSUD_NoScr	Probability of neurological damage due to MSUD without screening	0.100	0.075 – 0.125	Morton[154]
P_ND_MSUD_WithScr	Probability of neurological damage due to MSUD with screening	0.100	0.075 – 0.125	Morton[155]
P_SO_HCY_NoScr	Probability of spinal osteoporosis due to HCY without screening	0.509	0.350 – 0.668	Mudd[156], Scriver[157]
P_SO_HCY_WithScr	Probability of spinal osteoporosis due to HCY with screening	0.050	0 – 0.100	Mudd[158], Scriver[159]
P_TYR	Probability of tyrosinemia	0.00008		Department of State Health Services Data

149 Kyllerman M, Skjeldal OH, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations. *Mov Disord.* Jan 1994;9(1):22-30.

150 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

151 Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: natural history of 77 patients. *Am J Med Genet C Semin Med Genet.* Aug 15 2003;121C(1):38-52.

152 Kyllerman M, Skjeldal OH, Lundberg M, et al. Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations. *Mov Disord.* Jan 1994;9(1):22-30.

153 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

154 Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* Jun 2002;109(6):999-1008.

155 Ibid.

156 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

157 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

158 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

159 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

Table 3.3 Utility Estimates

Variable Name	Description	Estimated Average Utility	Range	Reference
U_CRF	Utility of having chronic renal failure	0.67	0.58-0.74	de Wit[160]
U_FP	Utility of receiving a false positive screen result	0.97	0.95-0.99	Venditti[161]
U_LT	Utility of liver transplant	0.67	0.58-0.74	Arguedas[162]
U_MR_ND_DD	Utility of mental retardation, neurological damage or developmental delay	0.56	0.50-0.60	Carrol and Downs[163]
U_SLD	Utility of severe liver disease	0.20	0.10-0.3	Arguedas[164]
U_SO	Utility of spinal osteoporosis	0.92	0.88-0.94	Yeh[165]
U_TX	Utility of being on treatment without complications	0.90	0.85-0.95	Venditti

0

160 de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. *Health Policy.* Jun 1998;44(3):215-232.

161 Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

162 Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol.* Mar 2003;98(3):679-690.

163 Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics.* May 2006;117(5 Pt 2):S287-295.

164 Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol.* Mar 2003;98(3):679-690.

165 Yeh J-Y. *Cost-effectiveness analyses of anti-resorptive agents for management of glucocorticoid-induced osteoporosis and fractures: Empirical estimates from the 1996--2004 MEPS data and longitudinal projection from Markov modeling* [Ph.D.]. United States -- Texas, The University of Texas at Austin; 2007.

3.8 Model Assumptions

The following assumptions were used while conducting the cost-effectiveness analysis.

1. A child can have only one metabolic disorder.
2. Testing is timely and testing methods are appropriate.
3. MS/MS is used for screening for the disorders included in this study.
4. In an individual experiencing more than one sequela, disutility caused by the most debilitating sequela also includes the disutility caused by other, less debilitating co-morbidities.
5. Newborn screening in Texas is universal.
6. The base case discount rate for costs and effectiveness (utilities) is 3%.

3.9 Cycle Length and Termination Condition

The cycle length was one year. One year was deemed as an appropriate cycle length since most clinical data on health outcomes was available on a yearly basis. Half cycle corrections were used for initial values of costs and utilities to avoid over estimation. One-time costs incurred in the first year of life such as cost of screening and diagnostic testing were not subject to half cycle correction. The Markov model terminated after 76 cycles which is equivalent to the estimate of average life expectancy.

3.10 Proposed Structure of Markov Model

This section includes a description of the proposed decision tree for estimating the cost-effectiveness of the expanded newborn screening program. The model is designed to estimate the incremental cost and effectiveness of only those disorders that were included in the screening panel *after* its expansion in 2007. Disorders that were already in the panel before the expansion are not included. The disorders included in the analysis were

grouped into seven categories based on their physiological characteristics. As shown in figure 3.3, the decision node for newborn screening has two main branches, one each for the expanded and the unexpanded screening programs. The branch representing the expanded program further has eight sub-branches arising from a chance node. Seven of the sub-branches represent the outcomes for the disorders being studied and the eighth branch represents outcomes for the healthy child. An infant can either be affected with one of the screened disorders or be healthy. A large majority of healthy infants should have a negative screen result while a small fraction may have a false positive screen result. Since the sensitivity of screening via tandem mass spectrometry is close to 1.0, we can choose not to include a branch for false negative results. The probability of testing positive for any one of the disorders is equal to the prevalence of that particular disorder. The sub-tree branches for unexpanded screening are *identical* to that for expanded screening. However, patients in the unexpanded screening branch are likely to experience greater morbidity and mortality because of delayed treatment. Hence, the probability values for each of the outcomes will be different for the expanded and unexpanded scenarios.

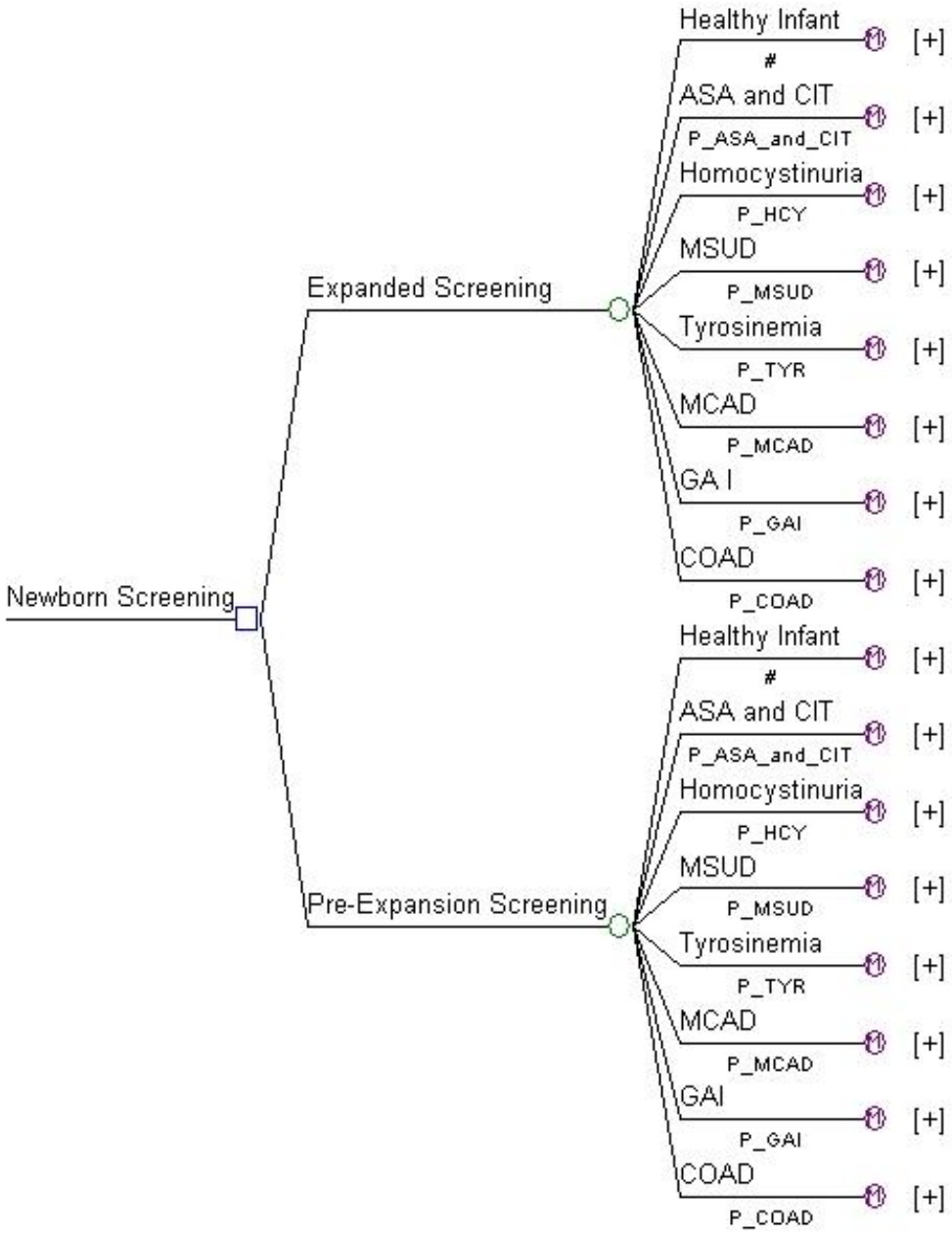

Figure 3.3 Decision Tree Showing the Branches of Expanded Newborn Screening Program

Note: # = probability of a negative result, which equals 1- (combined probability of all the other scenarios).

3.10.1 Disease Characteristics and Proposed Markov Structure

The Markov sub-tree for each of the disorders is based on the evidence in the literature. Overall, the literature for many of the disorders is sparse compared to that for some of the more common pediatric conditions. Some of the older studies include case reports that describe the natural history and disease progression among a small patient group seen at a single clinic. In the last few years, screening programs across the developed world have been expanded and there has been an increased interest in various aspects of screening. This interest is reflected in the literature as well with an increase in the number of good quality studies published in the recent years. The following sections describe the sequelae experienced by patients of inborn errors of metabolism. The Markov structure of the sub-tree representing each disorder is also presented. Expert opinion was sought whenever the information in the literature was insufficient.

3.10.1.1 Arginosuccinic Acidemia (ASA) and Citrullinemia (CIT)[166] [167]

ASA and CIT are both disorders of the urea cycle characterized by an inability to convert ammonia into urea. Infants with ASA lack the enzyme argininosuccinic acid lyase. This enzyme is responsisble for the breakdown of ammonia. Affected infants may appear normal at birth. However, due to a buildup of ammonia (hyperammonaemia), the affected child begins to experience developmental delay, mental retardation and neurological damage between the ages of 1-3 years. CIT presents itself as either an acute neonatal form or as a milder, late-onset form. Soon after birth, infants with the acute neonatal form suffer build-up of toxic substances such as ammonia and glutamine. Such

166 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

167 Drummond-Borg M. Metabolic Consultant Physician, Texas Department of State Health Services. In: Tiwana S, ed. Austin; 2007.

accumulation can lead to vomiting, loss of consciousness and death in an untreated patient. Even after timely intervention, prognosis for acute CIT is poor. Significant neurocognitive deficiencies are frequently observed.

Prior to the 1980s, patients of Urea Cycle Disorders such as ASA and CIT were treated with protein restriction alone. For the last two decades, an extensive therapy that includes supplements of arginine/citrulline and essential amino acids along with sodium phenyl acetate and sodium benzoate has been used for treating these patients. Experts agree that although survival has improved for urea cycle patients, rates of mental retardation tend to remain high.

Figure 3.4 represents the Markov states for ASA and CIT. The probability values used in the Markov sub-tree representing outcomes for screened versus unscreened patients of ASA and CIT were based on expert opinion.[168] Please note that the structure of the sub-tree is identical for screened and unscreened populations. However, unscreened patients may have greater likelihood of adverse outcomes. These differential probabilities will be included in the analysis. (Please refer to Tables 3.1 to 3.3 for variable description and model inputs.)

168 Ibid.

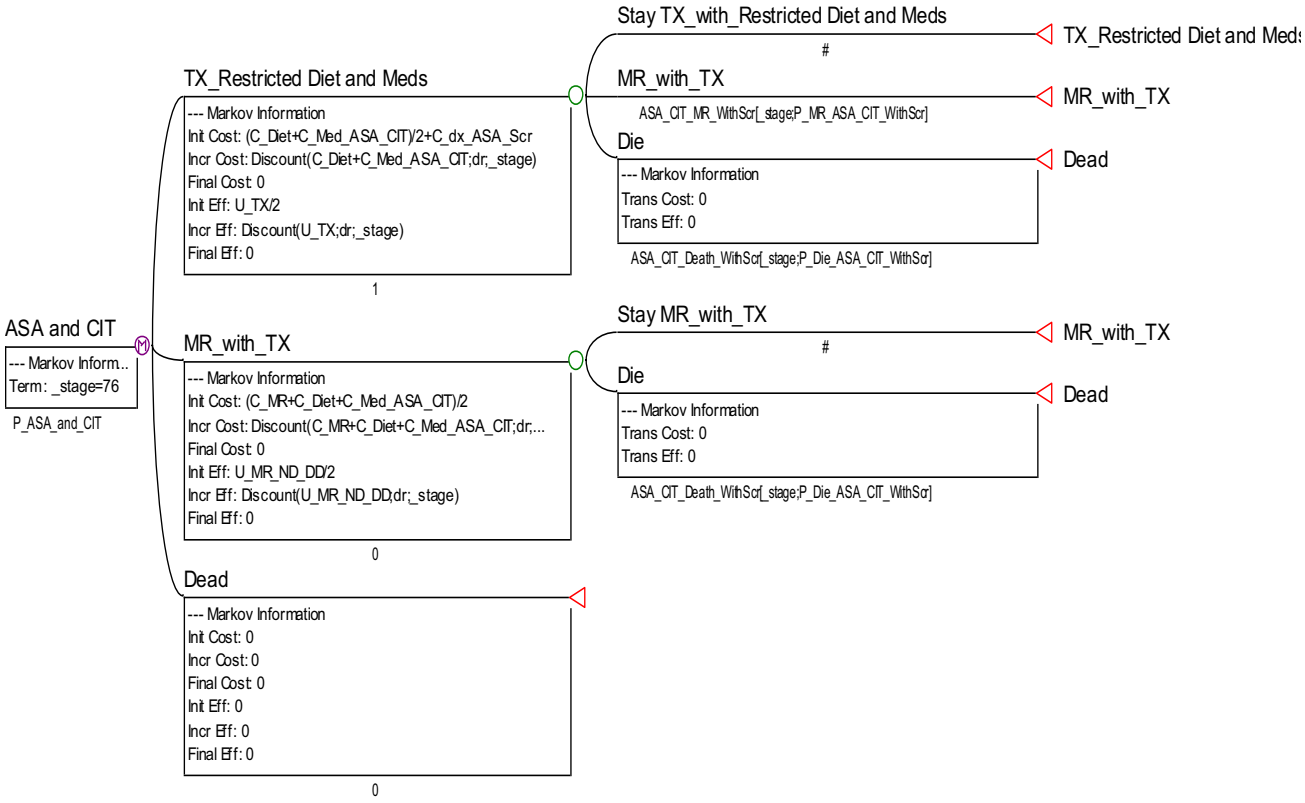

Figure 3.4 Markov Sub-tree for Arginosuccinic Acidemia (ASA) and Citrullinemia (CIT).

3.10.1.2 Homocystinuria (HCY)[169],[170]

HCY is another enzyme deficiency disorder that may be grouped with other Urea Cycle Disorders. Due to some unique sequelae of this particular disorder, it is being analyzed as a separate category. It is characterized by the build up of the amino acid homocystine. Patients may suffer mental retardation, lens abnormalities and skeletal abnormalities. Lens abnormalities can be corrected, so only occur in one cycle of the structure. Premature death may occur due to thromboembolism (blood clot formation). Treatment for HCY includes restricted diet, B6, B12 and Betaine supplementation and Cystine in some cases.

Figure 3.5 represents the Markov states for HCY. Please note that the structure of the Markov sub-tree is identical for screened and unscreened populations. However, unscreened patients may have greater likelihood of adverse outcomes. These differential probabilities were included in the analysis. (Please refer to Tables 3.1-3.3 for variable descriptions and model inputs.)

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169 Scriver CR, ed. *The metabolic & molecular bases of inherited disease.* 8th ed. New York: McGraw Hill; 2001.

170 Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet.* Jan 1985;37(1):1-31.

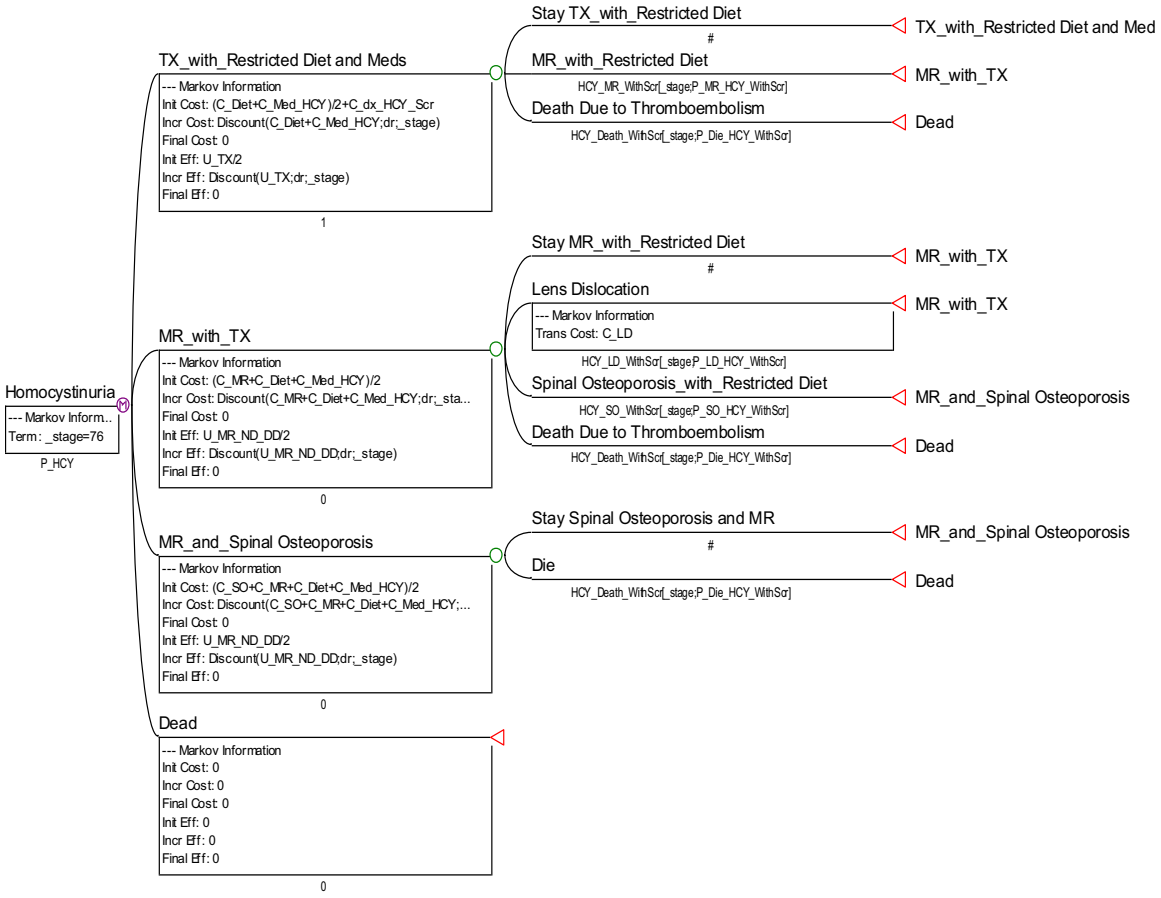

Figure 3.5 Markov Sub-tree for Homocystinuria.

3.10.1.3 Maple Syrup Urine Disease (MSUD)[171]

MSUD is characterized by enzyme deficiency in the metabolic pathway of branched-chain amino acids including leucine, isoleucine and valine. The urine of affected infants have a distinct "maple syrup" odor. Elevated blood levels of branched-chain amino acids, especially leucine, are associated with "metabolic intoxication". Neonates with classical MSUD begin to show signs of crisis within 48 hours of birth. It is common to witness seizures and cerebral edema by the age of 4 days. Coma and respiratory failure can occur within 7-10 days. Long term outcomes include neurological disorders and developmental delay. The gene responsible for MSUD is common in the Mennonite communities where incidence of this disorder may be as high as 1 in 200. Treatment includes special diet and thiamine supplements. One of the most comprehensive studies on the outcomes of MSUD has been conducted at the Clinic for Special Children in Pennsylvania. Study results were based on long-term follow up of 36 patients most of whom were from the Mennonite settlements in Eastern Pennsylvania. It was reported that significant morbidity may occur even in infants diagnosed within 6-10 days of age. A diagnosis after the age of 14 days results in severe morbidity and mortality.

Although it is possible to clinically diagnose MSUD within few hours of birth, it is more likely for specialists attending high-incidence patient populations to be able to do so. In states like Texas where MSUD may occur in 1 out of 200,000 infants, newborn screening may play an important role in prompt and definitive diagnosis of this disorder.

Figure 3.6 represents the Markov states for MSUD. Please note that the structure of the Markov sub-tree is identical for screened and unscreened populations. However,

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171 Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. *Pediatrics.* Jun 2002;109(6):999-1008.

unscreened patients may have greater likelihood of adverse outcomes. These differential probabilities will be included in the analysis. (Please refer to Tables 3.1-3.3 for model inputs.)

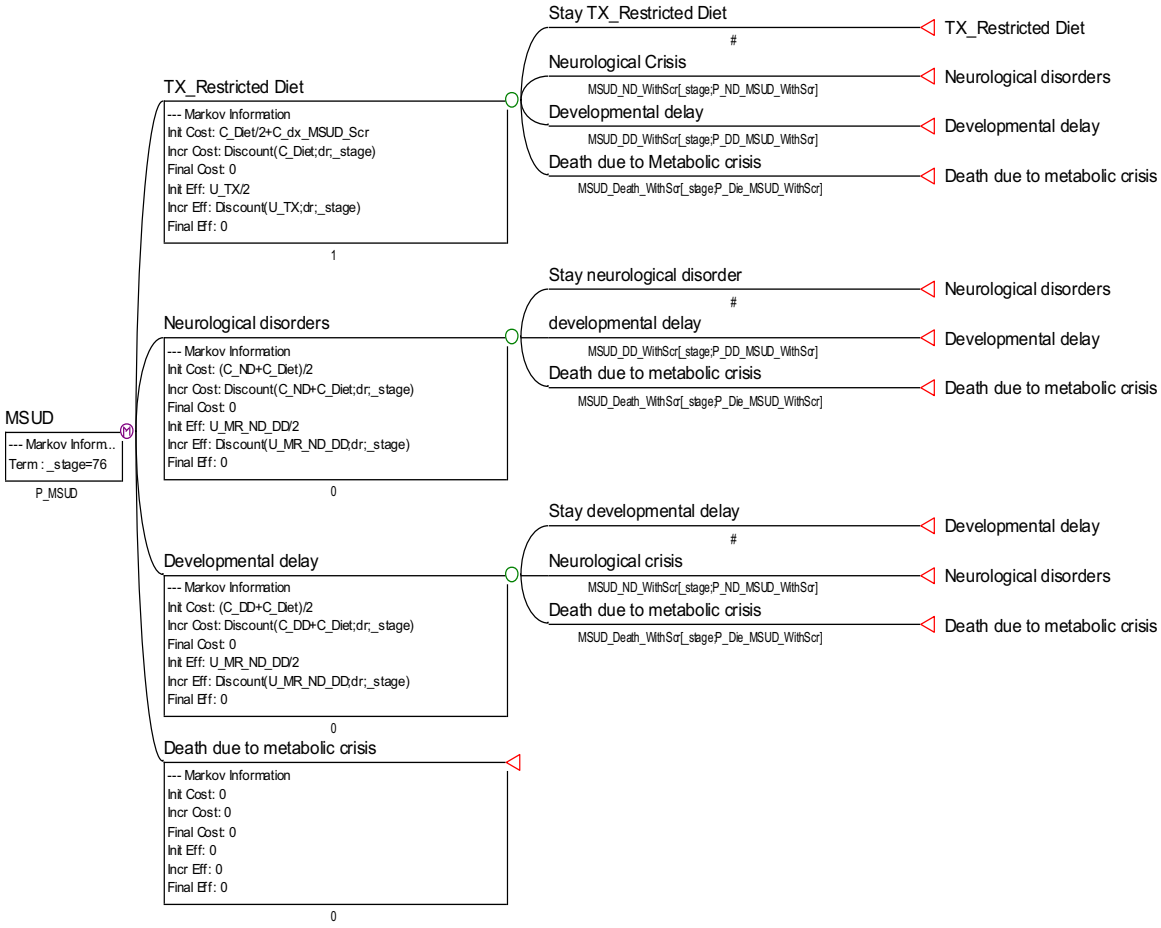

Figure 3.6 Markov Sub-tree for Maple Syrup Urine Disease

3.10.1.4 Tyrosinemia Type I (TYR)[172]

Tyrosinemia type I is an autosomal disorder characterized by severe liver damage because of enzyme deficiency in the tyrosine metabolic pathway. If left untreated, survival among tyrosinemia patients is extremely poor. Death occurs before the age of 10 years due to liver failure or hepatic carcinoma.

In 1991, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) was used in a trial for treating tyrosinemia type I . This new treatment proved effective in averting tyrosine degradation and the adverse outcomes associated with it. Since then, the prognosis for tyrosinemia type I patients has improved dramatically. In a 1998 study, outcomes of 176 patients treated with NTBC have been reported. Patients who received treatment before the age of two years were considered "early treatment group (n=101)" and those who received treatment after the age of 2 years were considered "late treatment group (n=75)." Overall, a total of 18 liver transplants were performed in the early treatment group. The reasons for transplant included poor response to NTBC treatment, progressive liver disease with suspected hepatic carcinoma, end stage liver disease and elective transplant. Of the 18 patients, 6 did not survive after the transplant. If patients receiving treatment before the age of six months are considered separately, then 10% of the patients in this group required liver transplants because of poor response to NTBC treatment. Half of these transplant recipients died because of complications.

In the late treatment group, many patients with a milder form of the disease were also included along with those who had severe complications. Liver transplant was required in 13/75 patients. Of those, 3 patients died due to complications related to the

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172 Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inherit Metab Dis.* Aug 1998;21(5):507-517.

transplant. Two other deaths were reported in the late treatment group because of other complications.

It is important to note that even in the absence of universal screening for tyrosinemia, an effective treatment plan was available for this disease. However, patients received this treatment only when they were diagnosed because of their clinical symptoms. Depending upon the severity of their disease, patients may present clinical symptoms early in life or may remain asymptomatic until much later. For the purpose of constructing a Markov sub-tree for tyrosinemia type I, it may be appropriate to use the combined data of both the late and early treated groups as an estimate of outcomes without universal screening. With newborn screening, infants with a positive diagnosis of tyrosinemia will start treatment as early as the first month of life. Therefore, study results for patients receiving treatment before the age of six months may be a reasonable estimate for patient outcomes in the presence of universal screening. Please refer to Tables 3.1-3.3 for model inputs. Figure 3.7 represents the Markov states for tyrosinemia.

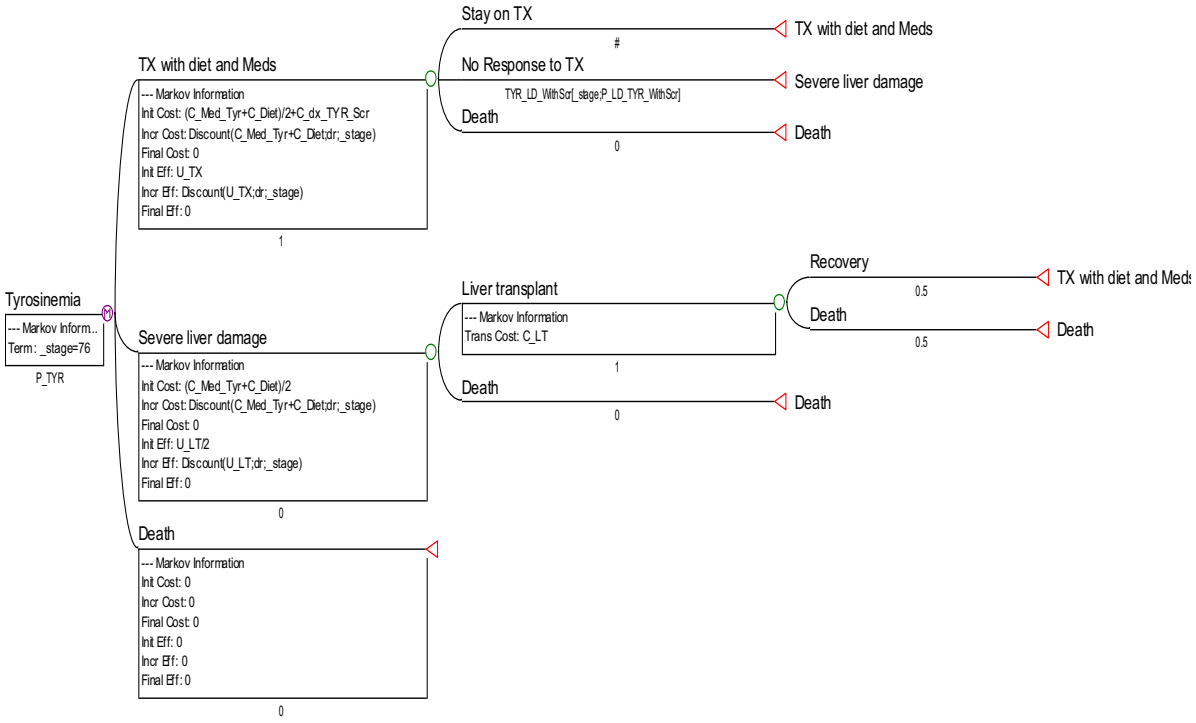

Figure 3.7 Markov Sub-tree for Tyrosinemia

3.10.1.5 MCADD and Other Fatty Acid Disorders[173],[174],[175]

Infants diagnosed with MCADD are unable to metabolize fatty acids. They primarily rely on carbohydrates for their energy needs. Most MCADD patients are started off with no treatment. A positive diagnosis of MCADD is followed by counseling of the parents. Parents are made aware of the dangers of prolonged fasting (greater than a few hours) in MCADD patients. They are also instructed to bring the child to the hospital if the child refuses to eat due to minor illness. The sick child may be given intravenous fluids in the hospital.

In a study of 59 children with MCADD, health care utilization and costs were compared between screened and unscreened groups. While only about 15% of the screened patients used inpatient services, inpatient admissions were significantly higher in the unscreened group ($p = 0.01$). This number was consistently higher for the unscreened groups. However, the average number of inpatients stays was similar for the two groups (about 1 per year) and the length of stay was also similar (2.6 days).[176] It has been reported in the literature that of the children who are hospitalized due to MCADD-related complications, one third may develop some type of developmental delay. About a third of those may suffer serious complications.[177] These estimates were used to construct the sub-tree for MCADD. In the absence of screening, about 25% of MCADD

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173 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

174 Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

175 Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

176 Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

177 Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

patients would die. Deaths can occur even in the screened population, primarily due to lack of adherence to treatment regimen (avoidance of prolonged fasting). In a recent article, 2 deaths were reported among 47 infants screened for MCADD, 1/47 had a severe episode of metabolic crisis and 2/47 had neonatal hypoglycemia.[178] Please refer to Tables 3.1-3.3 for model inputs. Figure 3.8 represents the Markov sub-tree for MCADD and other fatty acid disorders.

[178] Hsu HW, Zytkovicz TH, Comeau AM, et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. *Pediatrics.* May 2008;121(5):e1108-1114.

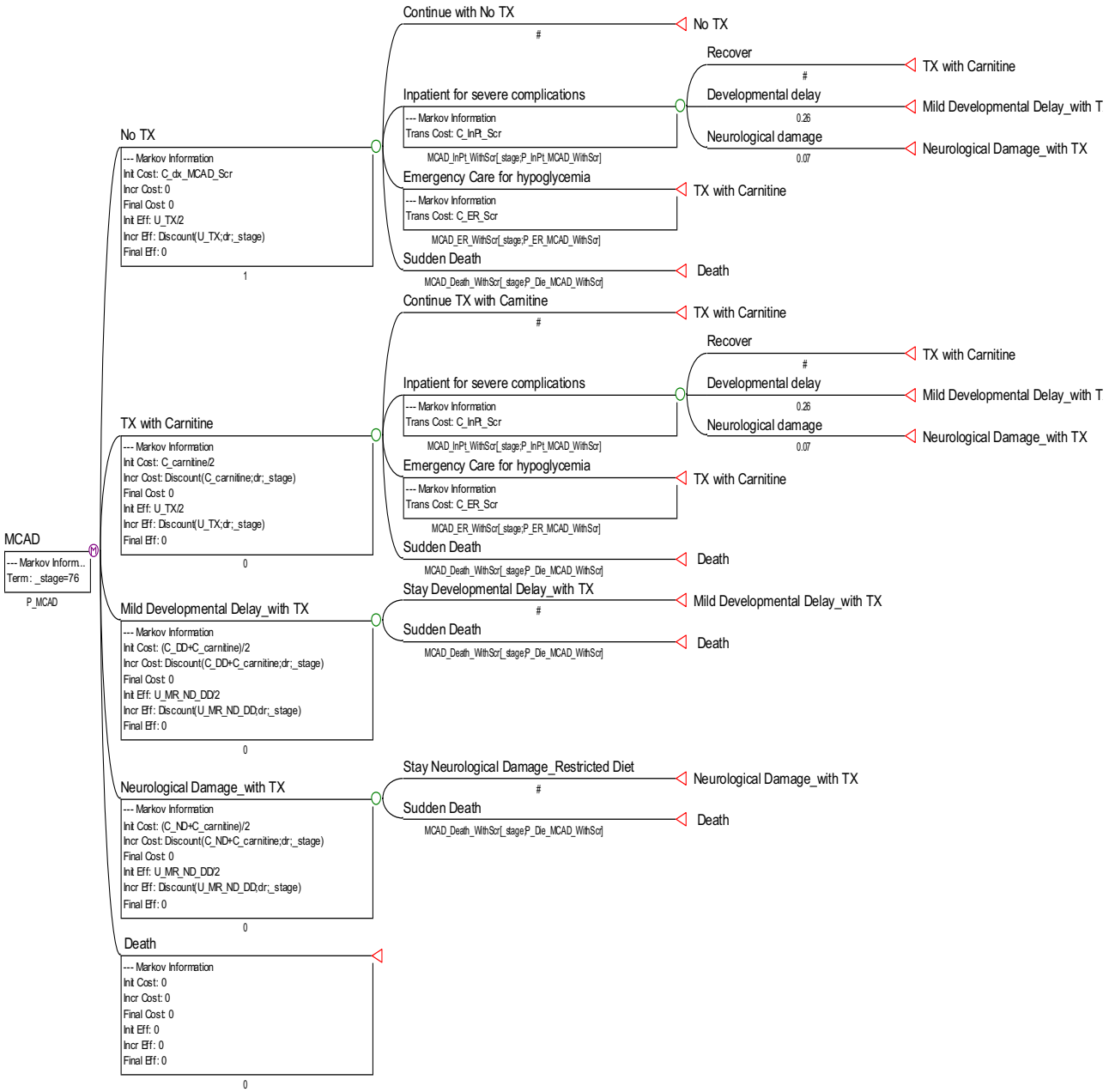

Figure 3.8 Markov Sub-tree for MCADD and Other Fatty Acid Disorders

3.10.1.6 Glutaric Acidemia Type I[179]

GA I is a disorder of the metabolic pathway for the amino acids lysine, hydroxylysine and tryptophan. The impact of a compromised metabolic pathway is compounded by a concurrent illness. Affected infants may present with acute stroke-like brain damage (striatal necrosis) between 6-18 months of age with majority of cases presenting between 6-14 months. The disease is also known as "Amish cerebral palsy" because of its high prevalence in this community of Lancaster County, Pennsylvania. At the time of clinical diagnosis, most patients have suffered irreparable damage to their brain and may remain disabled for life. In a study describing the natural history of 77 patients seen at the Clinic for Special Children in Pennsylvania, Strauss et al. emphasized the importance of early diagnosis via screening. They reported that timely intervention in asymptomatic GA I patients may reduce the occurrence of brain damage from as much as 90% to 35%.[180] These results have been used to allocate probabilities to the sequeale in the sub-tree for GA I.

Figure 3.9 represents Markov states for GA I. Please note that the structure of the Markov sub-trees is identical for screened and unscreened populations. However, unscreened patients may have greater likelihood of adverse outcomes. These differential probabilities will be included in the analysis. (Please refer to Tables 3.1-3.3 for model inputs.)

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179 Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type I glutaric aciduria, part 1: natural history of 77 patients. *Am J Med Genet C Semin Med Genet.* Aug 15 2003;121C(1):38-52.

180 Ibid.

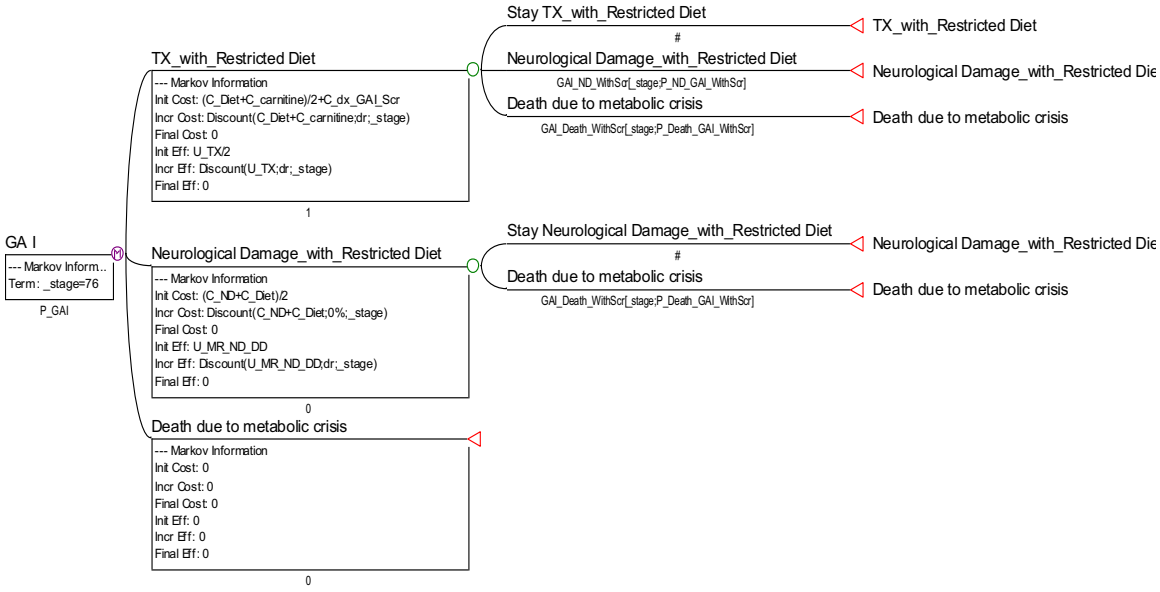

Figure 3.9 Markov States for Glutaric Acidemia Type I

3.10.1.7 Classical Organic Acid Disorders (IVA, MMA, PA)[181]

Classical organic acid disorders (COAD) are a group of three disorders namely isovaleric aciduria (IVA), propionic aciduria (PA) and methylmalonic aciduria (MMA). These disorders are characterized by an inability to metabolize one or more branched-chain amino acids such as leucine, isoleucine, valine, methionine and threonine. Treatment includes a special diet.

The Markov states for the affected infants are based on a 2006 study describing the long-term outcomes of classical organic acid disorders. In this study, Dionici-Vici and colleagues compared the outcomes for patients detected via clinical symptoms with those detected via newborn screening.

The clinical diagnosis group included 29 patients with either IVA or MMA or PA. The median age of diagnosis was 7 days of age. More than half (51%) of these patients experienced early mortality. Most of the deaths (40%) occurred before the age of 2 years. The survivors also experienced poor outcomes such as chronic renal failure (among those who had MMA), and neurocognitive impairment. There were 12 patients who survived with MMA. All of them experienced chronic renal failure after the age of 6 years. Progressive neurocognitive deterioration was observed in majority of the patients with all three disorders. In the long run, only 27% of the survivors had normal neurocognitive outcome. In order to accurately depict the prognosis for clinically diagnosed patients of classical organic acid disorders, a subset of these patients will be allocated to the Markov state of chronic renal failure along with neurological impairment.[182]

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[181] Dionisi-Vici C, Deodato F, Roschinger W, Rhead W, Wilcken B. 'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis.* Apr-Jun 2006;29(2-3):383-389.

[182] Ibid.

In the screened group (n=18), outcomes were better than the clinical diagnosis group. The median age of diagnosis was 4 days. There were two deaths (11%) and only one patient (5%) suffered chronic renal failure. Neurological impairment was observed in 31% of the survivors (n=16). Therefore, an estimated 27% of the total cohort (n=18) suffered neurological impairment. Please refer to Tables 3.1-3.3 for model inputs. Figure 3.10 represents the Markov states for COAD.[183]

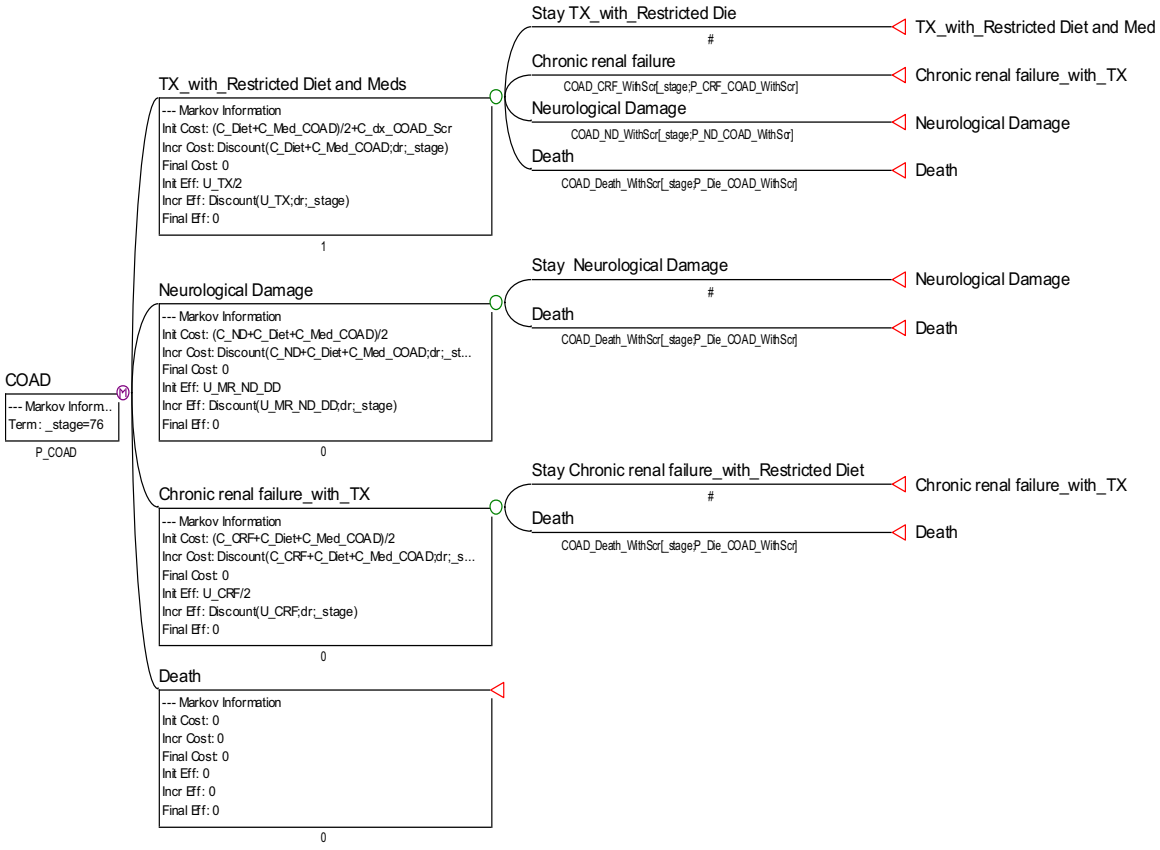

Figure 3.10 Markov Sub-tree for Classical Organic Acid Disorders

183 Ibid.

3.11 DEALING WITH UNCERTAINTY – SENSITIVITY ANALYSIS

It is common for decision models to include numerous parameters, each of which is estimated with certain inherent uncertainty. Sensitivity analyses must be conducted to account for the uncertainty in estimation. Results of a sensitivity analysis help decision makers in evaluating the robustness of the study results across various parameters. For large non-linear models such as the one being used in the current study, a standard sensitivity analysis is difficult to manage and may also introduce bias in estimation. Therefore a probabilistic sensitivity analysis using Monte Carlo simulation was used to account for uncertainty in the model parameters.

For most of the probability values used in the model, only point estimates were available from the literature. A clinically meaningful range was constructed around this point estimate. With the availability of only a mid point around which a high and low value was estimated, triangular distributions were assumed to be most suitable for representing uncertainty. Although it can be argued that some health states are worse than death and therefore should be given a negative value, this practice is rarely followed in cost-effectiveness analyses. The utility values used in this study were between 0 and 1.0, where 0 represented death and 1.0 represented perfect health.

Chapter Four - Results

This chapter includes the results for each of the study objectives. Data on Texas newborns, incidence of newly included disorders in the screening panel, cost of screening and confirmatory testing, cost of treatment and follow-up and detailed results of cost-effectiveness analysis (including one-way and probabilistic sensitivity analysis) are provided in this chapter.

4.1 RESULTS FOR OBJECTIVE 1

Demographic Characteristics of the Infant Population Served by the Texas Newborn Screening Program

The latest birth data for Texas newborns was available for 2005. Table 4.1 shows the most recent birth data (from 2005) divided by race and ethnicity for Texas newborns. Corresponding data for the United States births for the same year are also shown. The 2005 birth cohort for Texas was predominantly white (84.8%), followed by African Americans, Asian and Pacific Islanders and Native Americans. The US Census also recommends that demographic data should be based on at least two ethnicities: Hispanic and Non-Hispanic. Hispanics may belong to any race. Overall, the number of Hispanic births in Texas (49.5%) was nearly equal to that of the Non-Hispanic births (50.3%). This number is about twice that of the national average of Hispanic births (24.6%).

Table 4.1 2005 Birth Data by Race and Ethnicity: Texas Versus the United States

	White n (%)	**African American n (%)**	**Native American n (%)**	**Asian or Pacific Islander n (%)**	**Total**	**Hispanic n (%)**	**Non-Hispanic n (%)**
Texas	328,876 (84.8%)	44,402 (11.4%)	899 (0.23%)	13,679 (3.5%)	387,856	192,098 (49.5%)	194,908 (50.3%)
United States	3,275,613 (78%)	639,479 (15.2%)	44,831 (1.1%)	237,037 (5.6%)	4,196,960	1,033,444 (24.6%)	3,133,677 (74.7%)

4.2 RESULTS FOR OBJECTIVE 2

Incidence of Various Metabolic Disorders in Texas

The incidence data of various disorders was available for 2007 and is shown in Table 4.2. The 2007 incidence for ASA and CIT, HCY, MSUD, TYR and GA I was less than the incidence reported in the literature. Incidence of MCADD and other fatty acid disorders, and COAD was higher than the expected number. Estimated incidence was calculated for a birth cohort of 400,000 births in 2007. No cases were found for Tyrosinemia. With an incidence of 1/100,000 we were expecting that at least one case would have been diagnosed via newborn screening in Texas. In the absence of any reported cases of TYR in Texas for 2007, national incidence was used in calculations of costs and effectiveness related to the treatment of this disorder.

Table 4.2 Incidence of Various Disorders (Detected via MS/MS) in Texas in 2007

Disorder	Expected Incidence for 400,000 Estimated Births for 2007	Total Cases in 2007	Females (n)	Males (n)	White (n)	Hispanic (n)	Asian (n)	African American (n)
ASA and CIT	5	3	2	1	1	1	1	0
Homocystinuria	2	3	2	1	0	3	0	0
MSUD	2	1	1	0	0	1	0	0
TYR*	4	0*	0	0	0	0	0	0
MCADDD and other Fatty Acid Disorders (VLCAD, LCHAD)	27	30	13	17	19	9	0	2
GA-1	13	7	4	3	3	3	0	1
MMA, PA, IVA (COAD)	3	4	3	1	3	1	0	0
Total	56	48	25	23	26	18	1	3

*In the absence of any reported cases of TYR in 2007, published estimates were used for the incidence of TYR in cost-effectiveness calculations. For all other disorders, 2007 data for Texas was used.

4.3 RESULTS FOR OBJECTIVE 3

Cost of Screening and Confirmatory Testing

The cost of screening was $29.50 per screen, yielding a cost of $59.00 per infant for two screens that are conducted in the state of Texas. The cost of confirmatory testing (for infants who receive a positive screen result) varies by disorders. Confirmatory testing cost for some disorders like MCADD and other fatty acid disorders is much more expensive than that for others. This variation in cost is because of the nature of testing required to reach a confirmed diagnosis for a positive newborn screen. Table 4.3 shows the list of confirmatory tests conducted for each condition along with the average cost.[184] The number of false positives and cost of confirmatory testing for false positives is also shown. The overall cost of confirmatory testing for false positives was the highest for MCADD and other fatty acid disorders because of the high cost of testing and the high number of false positive newborn screen results.

[184] {, #122}

Table 4.3 Cost of Confirmatory Testing[185]

Disorder name	Confirmatory test(s)	CPT Code	Estimated Cost for Individual Test	Total Cost of Confirmatory Testing per case	False Positive Cases in 2007	Estimated Cost of False Positives
Arginosuccinic Aciduria/Citrullinemia	Plasma Amino Acids	82139	$140	$370	45	$16,650
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			
Homocystinurea	Homocystine Total	83090	$45	$220	205	$45,100
	Plasma Amino Acids	82139	$140			
	Suplemental Newborn Screening	83788	$35			
Maple Syrup Urine Disease	Plasma Amino Acids	82139	$140	$370	79	$29,230
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			
Tyrosinemia	Plasma Amino Acids	82139	$140	$370	291	$107,670
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			

[185] {, #122}

Table 4.3 Continued…

MCADDD and other fatty acid disorders	Acylcarnitine profile	82017	$110	$4,170	474	$1,976,580
	Carnitine Levels	82379	$80			
	MCADDD DNA Analysis	83890	$150			
	MCADDD Unknown Mutation	83890	$2,000			
	MCADDD Panel of 8 Mutations	83890	$850			
	Mitochondrial Beta Oxidation	88233	$750			
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			
Glutaric Acidemia Type I	Acylcarnitine profile	82017	$110	$340	93	$31,620
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			
Isovaleric Acidemia	Acylcarnitine profile	82017	$110	$340	170	$57,800
	Suplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			
Methylmalonic Acidemia/Propionic Acidemia	Acylcarnitine Profile	82017	$110	$420	42	$17,640
	Carnitine Levels	82379	$80			
	Supplemental Newborn Screening	83788	$35			
	Urine Organic Acids	83918	$195			

4.4 RESULTS FOR OBJECTIVE 4

Average Direct Medical Costs of Screening and Follow-up

Table 4.4 includes the average costs, average QALYs and ICERs for each of the disorder categories with or without screening at 0%, 3% and 5% discount rate. We had hypothesized that the average direct medical costs associated with treatment and follow-up of patients in the screening (expanded screening) category will exceed the average direct medical costs for those in the without screening (pre-expansion) strategy. As shown in table 4.4, costs associated with expanded screening strategy exceed those associated with pre-expansion strategy, except in case of HCY. So hypotheses H4.1, H4.3 – H4.7 are accepted and hypothesis H4.2 is rejected.

4.5 RESULTS FOR OBJECTIVE 5

Average QALYs.

Table 4.4 includes the average costs, average QALYs and ICERs for each of the disorder categories with or without screening at 0%, 3% and 5% discount rate. We had hypothesized that the average QALYs for patients in the screening category will exceed the average direct QALYs for those in the pre-expansion strategy. Table 4.4 supports these hypotheses. So hypotheses Ho5 A1 – Ho5 A7 are accepted.

Table 4.4. Average Cost and Effectiveness by Disorder at 0%, 3% and 5% Discount Rate

Disorder	Discount Rate	Cost with Screening	QALYs with Screening	Costs without Screening	QALYs Without Screening	ICER
ASA and CIT	0%	$1,858,587.90	33.78	$1,455,540.31	26.33	54,100.35
	3%	*$767,266.22*	*14.02*	*$605,811.70*	*11.03*	*53,998.17*
	5%	$520,300.84	9.55	$413,476.69	7.56	53,680.48
HCY	0%	$711,471.80	59.74	$837,816.55	45.44	Dominant
	3%	*$286,263.31*	*24.08*	*$335,448.14*	*18.53*	*Dominant*
	5%	$190,269.96	16.03	$222,290.79	12.43	Dominant
MSUD	0%	$376,141.93	61.34	$89,994.38	13.74	6,011.50
	3%	*$150,910.26*	*24.70*	*$37,439.39*	*5.74*	*5,984.75*
	5%	$100,092.02	16.42	$25,587.85	3.93	5,965.10
TYR	0%	$891,069.00	67.19	$214,050.25	16.27	13,295.73
	3%	*$363,787.77*	*27.70*	*$86,440.83*	*6.70*	*13,206.99*
	5%	$244,856.90	18.78	$57,657.12	4.54	13,146.05
MCADDD	0%	$411,262.22	46.94	$351,892.31	35.31	5,104.90
	3%	*$158,373.64*	*20.36*	*$143,077.69*	*15.25*	*2,993.33*
	5%	$102,668.00	14.09	$96,268.78	10.61	1,840.98
GA I	0%	$675,749.24	57.65	$76,787.93	3.92	11,147.61
	3%	*$374,870.87*	*23.30*	*$67,487.43*	*3.56*	*15,571.60*
	5%	$306,724.33	15.55	$62,274.50	3.35	20,036.87
COAD	0%	$505,306.60	55.68	$380,682.52	34.92	6,003.09
	3%	*$200,339.86*	*22.74*	*$149,897.00*	*14.54*	*6,151.57*
	5%	$131,797.86	15.27	$98,237.95	9.91	6,261.18

4.6 RESULTS FOR OBJECTIVE 6

ICERs for Each Disorder Category and Results of the Cost-effectiveness of Expanded Newborn Screening Using MS/MS as Compared to Unexpanded Screening Using a Cost-utility Analysis (CUA)

The ICER for all disorder categories was less than the Rc of $50,000, except in case of ASA and CIT where it exceeded the Rc (Table 4.4). Therefore H6.1 is rejected and H6.2-H6.7 are accepted**.**

As shown in Table 4.5, the ICER for expanded screening versus pre-expansion screening was $12,347.89/QALY at the base discount rate of 3%. At the base case estimate, expanded screening costs an additional $40.90 and results in an additional 0.00331 QALYs.

Tables 4.6 and 4.7 show the results of the cost-effectiveness analyses at 0% and 5% respectively. Therefore, expanded screening was cost effective as compared to pre-expansion screening.

Table 4.5 Overall Cost-effectiveness of Screening Versus No Screening at 3% Discount Rate

Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Cost/ Effectiveness	Incremental Cost-Effectiveness Ratio (ICER)
Pre-Expansion Screening	$103.30		30.69632		$3.37	
Expanded Screening	$144.20	$40.90	30.69963	0.00331	$4.70	$12,347.89

Table 4.6 Overall Cost-effectiveness of Screening Versus No Screening at 0% Discount Rate

Strategy	Cost	Incremental Cost	Effectiveness QALY	Incremental Effectiveness	Cost/ Effectiveness	Incremental Cost Effectiveness Ratio (ICER)
Pre-Expansion Screening	$163.30		75.9858		$2.15	
Expanded Screening	$257.90	$94.50	75.9941	0.0083	$3.39	$11,419.31

Table 4.7 Overall Cost-effectiveness of Screening Versus No Screening at 5% Discount Rate

Strategy	Cost	Incremental Cost	Effectiveness (QALY)	Incremental Effectiveness	Cost/ Effectiveness	Incremental Cost Effectiveness Ratio (ICER)
Pre-Expansion Screening	$89.70		20.48140		$4.38	
Expanded Screening	$118.70	$29.00	20.48358	0.00218	$5.79	$13,312.50

4.7 RESULTS OF ONE-WAY SENSITIVITY ANALYSES TORNADO DIAGRAMS

This section describes the results of one way sensitivity analyses performed on the study variables. A preliminary sensitivity analysis using a tornado diagram was performed for each of the variable categories (costs, probabilities and utilities). Another sensitivity analysis was performed just for discount rate since this variable did not belong to any of the above mentioned categories. A final tornado diagram was created with the top few most influential variables from each category.

As shown in Fig 4.1, the ICER for expanded screening varies between $11,418/QALY and $13,311/QALY with variations in the discount rate from 0% to 5%. Within the cost category, the most influential cost variables were yearly cost of medications for Tyrosinemia, yearly cost of special diet, yearly cost of carnitine supplementation, yearly cost of neurological damage and the yearly cost of medication for ASA and CIT (Figure 4.2). Within the probability category, probabilities of death due to ASA and CIT with and without screening were among the most influential variables. Probability of neurological damage due to GA I with and without screening, and probability of being clinically diagnosed with tyrosinemia were other important variables (Figure 4.3). Within the utility category, the utility value of being on restricted diet was the most influential variable followed by the utility value of mental retardation, neurological damage and developmental delay, and utility value of having chronic renal failure respectively (Figure 4.4).

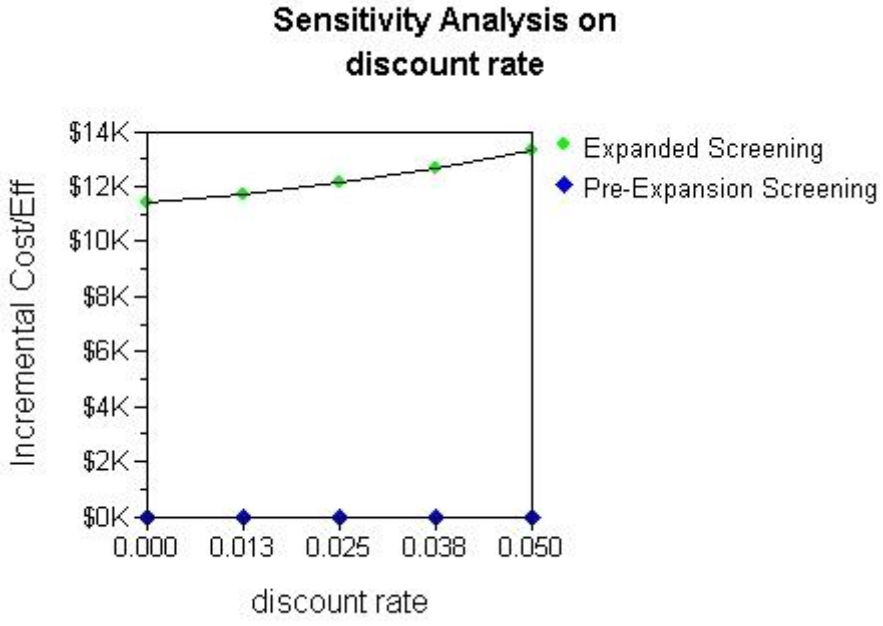

Figure 4.1 Impact of Various Cost Categories on the Results of Cost-effectiveness Analysis

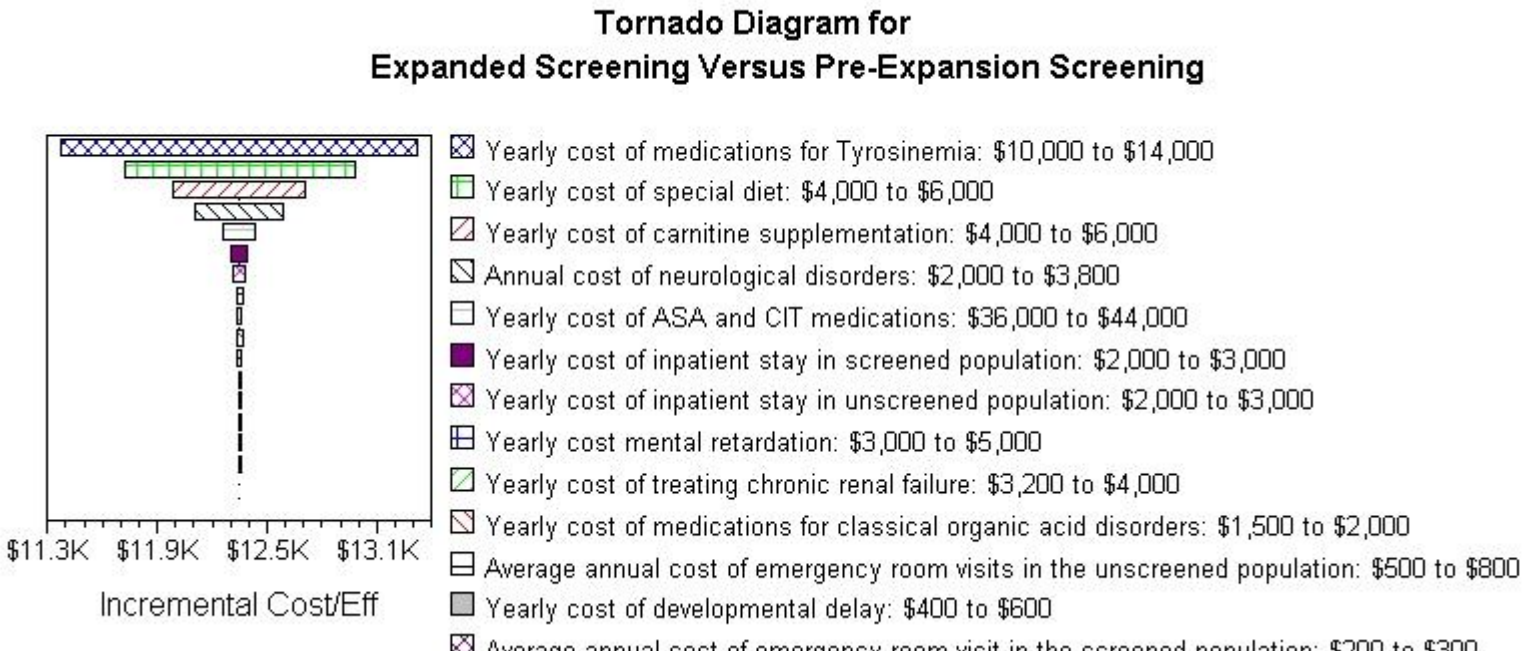

Figure 4.2 Impact of Various Cost Categories ($) on the Results of Cost-effectiveness Analysis

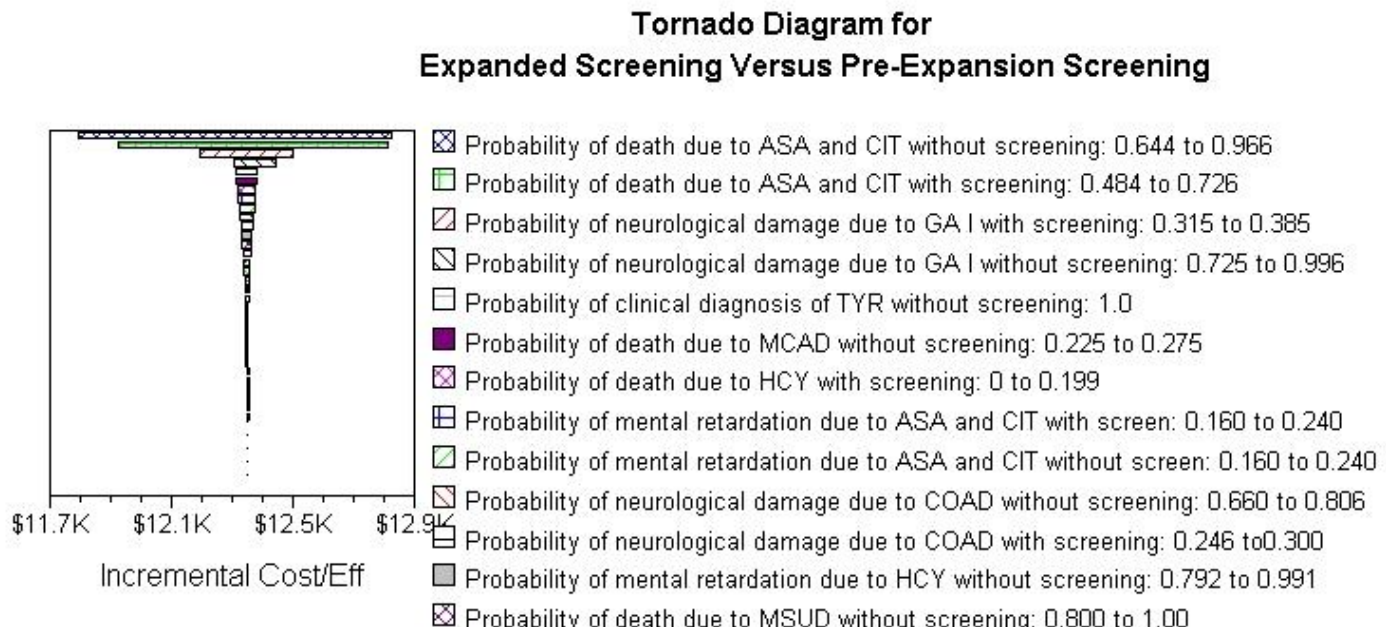

Figure 4.3 Impact of All Probability Values on the ICER

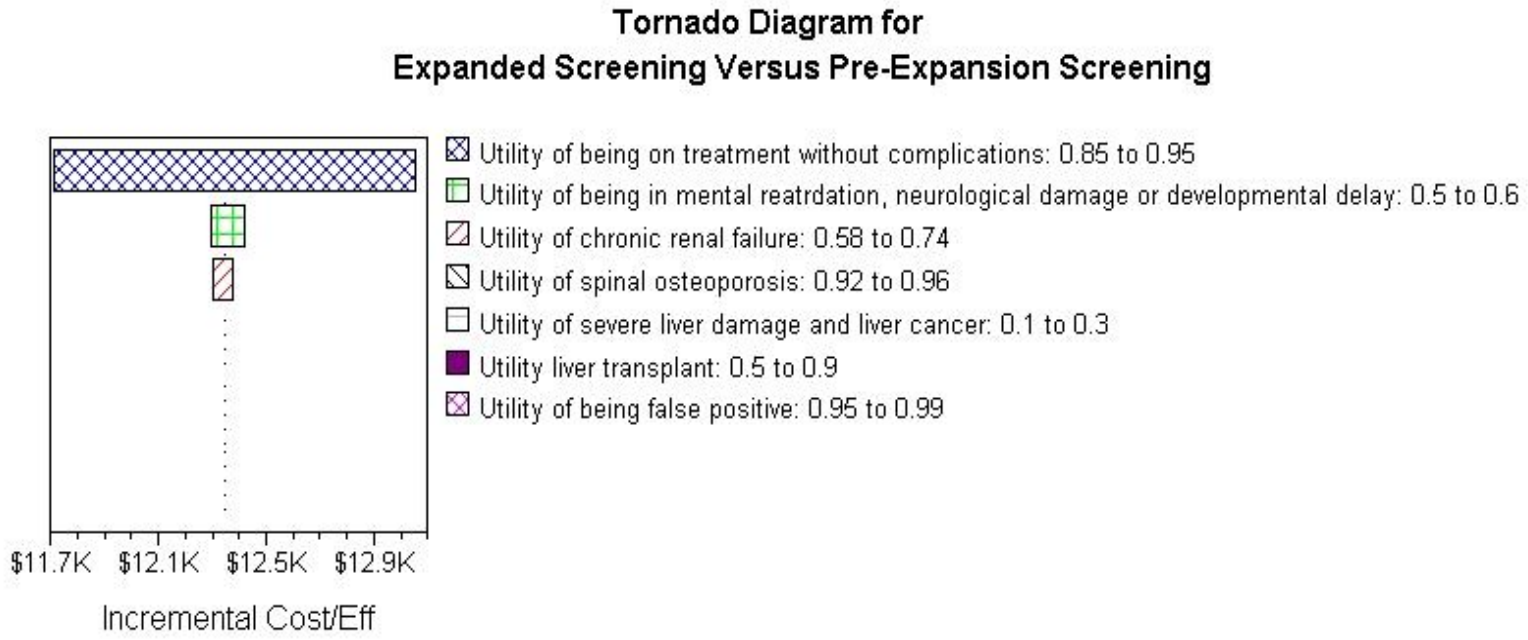

Figure 4.4 Impact of All Utility Values on ICER

Figure 4.5 shows the impact of the top few variables from each category on the results of the cost-effectiveness analysis. Yearly cost of medications for Tyrosinemia was the most influential variable, followed by the utility of treatment without complications. Other important variables were yearly cost of special diet, probability of death with and without screening in ASA and CIT, and yearly cost of carnitine supplementation.

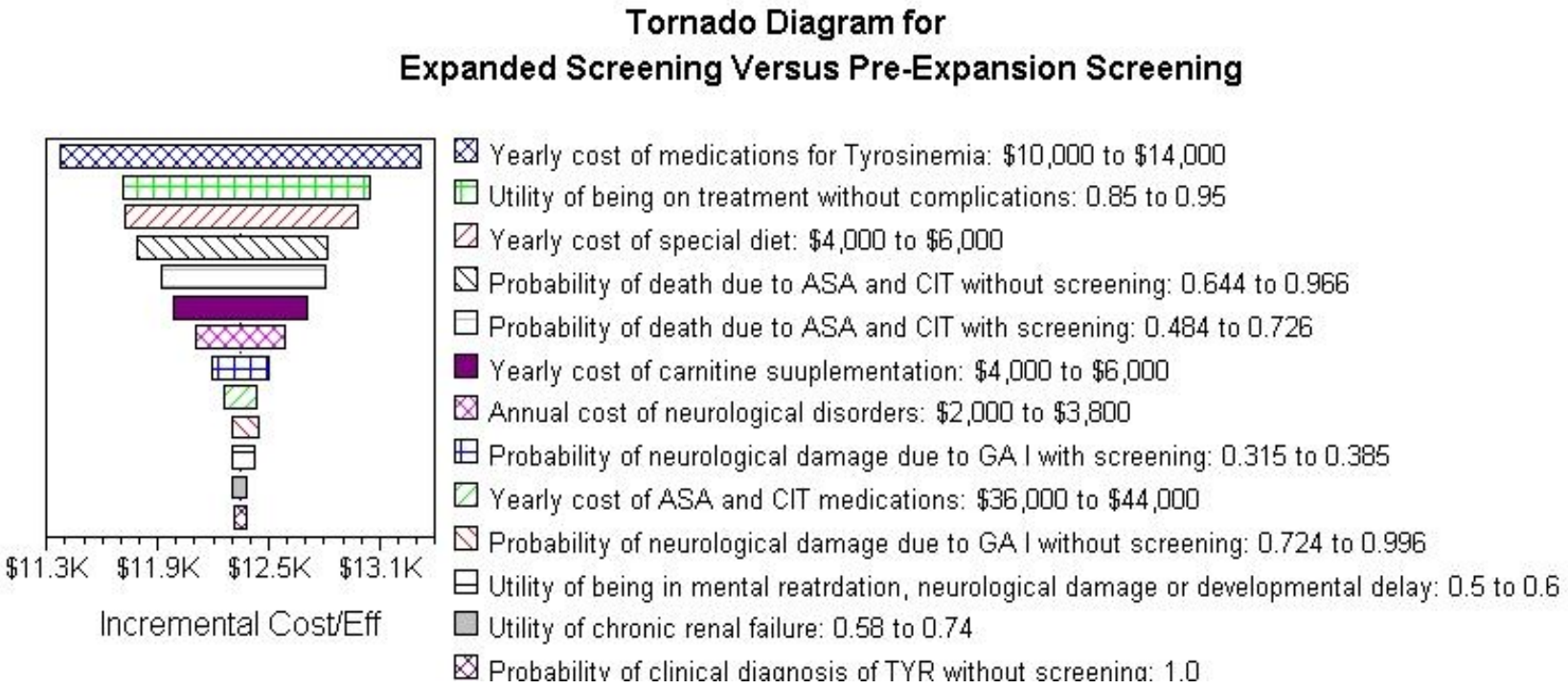

Figure 4.5 Impact of Top Few Variables from Each Category (Costs are in $)

4.8 Results of Probabilistic Sensitivity Analysis

Figure 4.6 shows the cost-effectiveness scatterplot obtained with a probabilistic sensitivity analysis. The mean value of cost for expanded screening was $169 (SD $28.87; range $120-$285). The mean effectiveness for expanded screening was 35.224 QALYs (SD 9.971 QALYs; range 20.568-74.451 QALYs). For pre-expansion screening, mean cost was $146 (SD $23.20; Range $107 - $239). The mean effectiveness for pre-expansion screening was 35.222 QALYs (SD 9.970 QALYs; Range 20.567 – 70.446 QALYs). A majority of the data points (97.5%) for expanded screening are at or below a cost of $244 and effectiveness of 61.098 QALYs. For pre expansion screening, 97.5% of the data points are at or below a cost of $206 and effectiveness of 61.094 QALYs. Therefore, on an average, expanded screening was associated with higher costs and slightly higher QALYs.

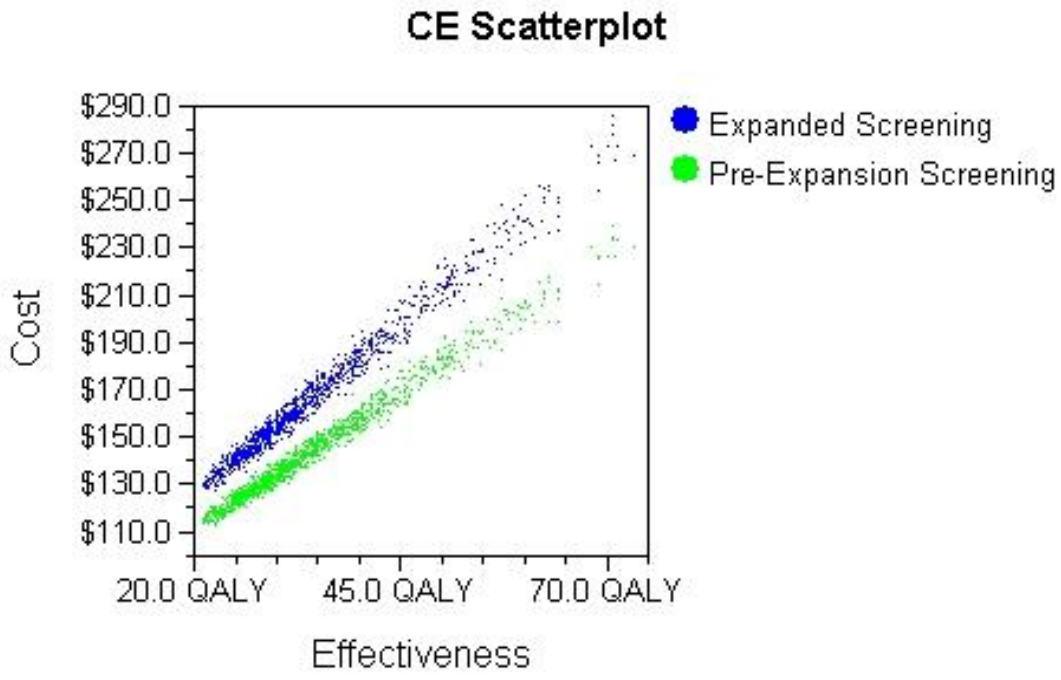

Figure 4.6 Cost-effectiveness Scatterplot Obtained from Monte Carlo Simulation

Figure 4.7 shows the acceptability curve for a willingness-to-pay threshold of $50,000 per QALY. Data points from the acceptability curve are presented in Table 4.8. These results show that at a WTP of $13,000/QALY, expanded screening (as compared to pre-expansion screening) is cost-effective for 100% of the iterations of the probabilistic sensitivity analysis. On the other hand, if the WTP is only $9,000/QALY, pre-expansion screening is cost-effective for 100% of the iterations (as compared to expanded screening). In other words, if a payer is willing to pay at least $13,000/QALY, then he/she would always choose expanded screening for any of the ranges used in our sensitivity analyses. Conversely, if the payer is only willing to pay up to $9,000/QALY then he/she would choose the pre-expansion screening for any of these ranges.

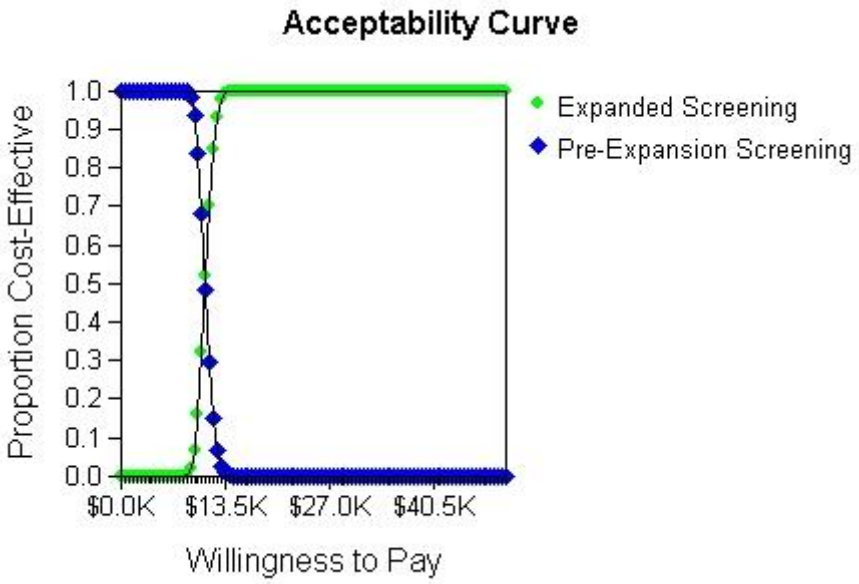

Figure 4.7 Acceptability Curve Obtained from Monte Carlo Simulation

Table 4.8 Acceptability Curve: Proportion Cost-effective for Each Screening Strategy

Willingness to Pay	Proportion Cost-effective for Expanded Screening	Proportion Cost-effective for Pre-expansion Screening
$9,000	0	1
$9,500	0.1	0.9
$10,000	0.2	0.8
$10,500	0.3	0.7
$11,000	0.5	0.5
$11,500	0.7	0.3
$12,000	0.8	0.2
$12,500	0.9	0.1
$13,000	1	0

Table 4.9 shows a summary of all the hypotheses that were tested in this study. Hypothesis H4.2 was rejected because based on our estimates, direct medical costs associated with screening of HCY were lower than the direct medical costs associated with no screening. Hypothesis H6.11 was also rejected because the ICER of expanded screening for ASA and CIT ($53,998.17/QALY) was slightly higher than the Rc of $50,000/QALY. All other hypotheses were accepted.

Table 4.9 Hypothesis Summary

Hypothesis	**Accepted**	**Rejected**
H4.1 Cost ASA_CIT expanded screening ≥ Cost ASA_CIT pre-expansion screening	√	
H4.2 Cost HCY expanded screening ≥ Cost HCY pre-expansion screening		√
H4.3 Cost TYR expanded screening ≥ Cost TYR pre-expansion screening	√	
H4.4 Cost MCADDD expanded screening ≥ Cost MCADDD pre-expansion screening	√	
H4.5 Cost GA I expanded screening ≥ Cost GA I pre-expansion screening	√	
H4.6 Cost MSUD expanded screening ≥ Cost MSUD pre-expansion screening	√	
H4.7 Cost COAD expanded screening ≥ Cost COAD pre-expansion screening	√	
H4.8 Overall direct medical costs expanded screening ≥ Overall direct medical costs pre-expansion screening	√	
H5.1 QALYs ASA_CIT expanded screening ≥ QALYs ASA_CIT pre-expansion screening	√	
H5.2 QALYs HCY expanded screening ≥ QALYs HCY pre-expansion screening	√	
H5.3 QALYs TYR expanded screening ≥ QALYs TYR pre-expansion screening	√	
H5.4 QALYs MCADDD expanded screening ≥ QALYs MCADDD pre-expansion screening	√	
H5.5 QALYs GA I expanded screening ≥ QALYs GA I pre-expansion screening	√	
H5.6 QALYs MSUD expanded screening ≥ QALYs MSUD pre-expansion screening	√	
H5.7 QALYs COAD expanded screening ≥ QALYs COAD pre-expansion screening	√	
H5.8: Overall QALYs expanded screening ≥ Overall QALYs pre-expansion screening	√	
H6.1: ICER ASA_CIT expanded screening versus pre-expansion screening ≤ Rc		√
H6.2: ICER HCY expanded screening versus pre-expansion screening ≤ Rc	√	
H6.3: ICER TYR expanded screening versus pre-expansion screening ≤ Rc	√	
H6.4: ICER MCADDD expanded screening versus pre-expansion screening ≤ Rc	√	
H6.5: ICER GA I expanded screening versus pre-expansion screening ≤ Rc	√	
H6.6: ICER MSUD expanded screening versus pre-expansion screening ≤ Rc	√	
H6.7: ICER COAD expanded screening versus pre-expansion screening ≤ Rc	√	
H6.8: Overall ICER expanded screening versus pre-expansion screening ≤ Rc	√	

Chapter Five - Discussion

This chapter is aimed at providing a discussion of the study results and possible explanations for the findings. Limitations of the current study and potential topics for future research are also discussed here.

5.1 Demographic Characteristics of the Infant Population Served by the Texas Newborn Screening Program

Texas accounts for nearly 8% of the total US population. With a 12% increase in population from 2000 to 2006, it is also one of the fastest growing states. The National Newborn Screening and Genetic Resource Center (NNSGRC) maintains a record of birth data by race and ethnicity for each of the states. The latest data available is for 2005. For Texas, the number of births when categorized by ethnicity, are nearly equally divided between Hispanics and non-Hispanics. However, the racial classification of the 2005 Texas birth data shows that nearly 85% of the newborns were white. This implies that infants classified as White could be of either Hispanic or non-Hispanic ethnicity. Further, those classified as Hispanic may belong to any race. Although the NNSGRC data follows the same classifications as that of the US Census, birth certificate data is obtained by self reports from the infant's family. It is common to encounter inconsistencies between these two sets of data. As seen in border states like Texas, "Hispanic" may also be used as a race and not as an ethnicity. Such discrepancies make it problematic to reliably allocate the birth data to discrete racial or ethnic categories. Study results do reflect that the percentage of Hispanic births in Texas is nearly twice that of the national average which may be attributed to the large population of individuals of Hispanic origin in the state. These numbers may be comparable with the demographic distribution of other states like California that share similar characteristics with Texas.

However, the results cannot be generalized to many other states in the country where the Hispanic population is small.

5.2 Incidence of Various Disorders in 2007 (After the Expansion of the Screening Program)

The disorder group with the highest incidence in 2007 was MCADDD and other fatty acids. With 30 diagnosed cases, the combined incidence of this group of disorders is estimated at 1 in 13,300 in Texas. Incidence for MCADDD alone was at 1 in 20,000 which is slightly lower than the national average of 1 in 17,000 reported by Grosse et al. in 2006.[186] Other disorders were less prevalent with 0-7 cases detected in 2007. The incidence of most disorders is a little higher or lower than the published numbers. There were no cases reported for Tyrosinemia in 2007 which does seem somewhat unexpected. With an incidence of 1 in 100,000, we were expecting that at least one case of Tyrosinemia would have been detected by newborn screening. Absence of any new cases of Tyrosinemia in the 2007 birth cohort could be a chance occurrence or could also be because of false negative screen results. Incidence of all disorders may fall closer to published estimates over the long term. Since none of the disorders being studied are thought to occur more frequently in either gender, the observed disparities in occurrence by gender (for 2007 data) may also become smaller over the long term.

5.3 Cost of Screening and Confirmatory Testing

The cost of screening in Texas is lower than that in many other states. This difference is largely due to variations in allocation of federal funding for running state programs like newborn screening. Cost estimates for confirmatory testing were obtained from the Institute of Metabolic Disease at the Baylor University Medical Center in

[186] {Grosse, 2006 #120}

Dallas, Texas. The average cost of confirmatory testing was estimated at $1,000. The Schoen study also used an estimate of $1,000 for the cost of false positive screen results for most of the disorder categories. However, they only allocated $200 for a false positive screen for MCADDD.[187] Our study results show that confirmatory testing for MCADDD and other fatty acid disorders is actually much more expensive (approximately $4,000 per case) than that for some of the other conditions. Detailed genetic analysis for identifying specific gene mutations contribute to the higher cost.

5.4 AVERAGE COST OF FOLLOW-UP AND TREATMENT FOR EACH DISORDER:

For most of the disorders, expanded screening is associated with higher treatment and follow-up costs. This can be explained by the increased life expectancy of patients detected early because of screening. Once they are diagnosed for a certain condition, patients need to be on special diet and other treatment for the rest of their lives. Early death may frequently be an outcome for unscreened patients. Since the current study included only direct medical costs, there are no costs associated with loss of productivity due to mortality. As a result, life-time costs for screened patients tend to be higher than those diagnosed post-symptomatically.

5.5 AVERAGE QALYS

The average quality adjusted life years (QALYs) for the screened groups are higher than those for the unscreened group. Screening typically leads to earlier diagnosis and treatment. With timely diagnosis and careful disease management, it is now possible for patients with metabolic disorders to lead relatively healthy lives. Conversely, patients diagnosed post-symptomatically (in the unscreened population) may have a higher risk of mortality and poorer disease prognosis, which contribute to fewer QALYs.

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[187] {Schoen, 2002 #19}

5.6 COST-EFFECTIVENESS OF EXPANDED NEWBORN SCREENING

As shown by the results of CUA analysis, expanded screening may cost an additional amount of $12,000/QALY at the base discount rate of 3%. Although the absolute difference in the effectiveness of the two strategies in relatively small at 0.00331 QALYs, it can potentially make a significant difference for the infants detected with one of the disorders. The ICER of expanded versus pre-expansion screening was compared with the commonly used threshold of $50,000/QALY. It may be argued that the threshold of $50,000 may not be representative of the very specific costs and outcomes related to disease states. Depending upon the nature of the health condition being studied, this value may be too high or too low. Further, it may be more practical to use a range for an acceptable value of ICER instead of an absolute value of $50,000/QALY. Use of a range of acceptable ICER values allows for the inclusion of other factors like burden of disease and imprecise estimation of costs and QALYs. The use of disease specific ICERs may be more feasible for conditions that have been studied extensively. Economic analyses of newborn screening are still relatively rare and a threshold ICER for this group of diseases may become clearer in the future.

For ASA and CIT, screening costs an additional $53,998/QALY at the base rate of 3%. This is higher than the WTP of $50,000 per QALY. One of the factors responsible for the relatively higher cost/QALY for ASA and CIT is the very high cost of treatment for these disorders. As per expert opinion, although screening results in higher survival among ASA and CIT patients, rates of mental retardation tend to remain high among the survivors. Therefore, quality of life for the survivors is poor overall. For HCY, screening not only costs less, but it also results in greater QALYs. Therefore, it is the dominant strategy for HCY. These results may be explained by the reduced likelihood of adverse outcomes in the screened group. A vast majority of the unscreened

patients of HCY are at risk of lens dislocation and chronic skeletal abnormalities as they grow older. These complications can result in significant direct medical costs and reduced quality of life. In contrast, only a few of the screened patients run the risk of lens dislocation or spinal osteoporosis, thereby resulting in reduced costs and better quality of life. For MSUD, there is a stark contrast in the QALYs for screened versus unscreened patients. This can be explained by the extremely high mortality in the first two years of life for children who may be diagnosed late. As a result, the quality of life for the dead members of the unscreened group is zero. This contributes to the overall low QALYs in the unscreened group. Yet, the ICER for screening versus no screening for MSUD ($5,900/QALY) is well below the common threshold of $50,000/QALY.

After HCY, MCADD is the second most cost-effective condition to screen for. Relatively low treatment costs and high prevalence of this disorder contribute to the economic viability of screening for this disorder. The ICER of $2,993/QALY is lower than some of the published estimates. Possible reasons for this difference could be the use of different model inputs.

For MSUD, Tyrosinemia and GA I, the difference between QALYs for the screened and unscreened groups is large. Screening for each of these conditions is cost-effective with ICERs ranging from $5,900 to $15,500/QALY.

Screening for COAD is also cost-effective with the ICER for screened group at $6,151/QALY. Timely intervention is crucial in this group of disorders and patients can enjoy good quality of life without incurring extremely high treatment costs.

5.7 COMPARISON WITH OTHER STUDIES

Table 5.1 Summary of recent economic analyses of newborn screening in North America

Year (Section)	Author(s)	Type of Analysis	Conditions studied	Main findings
2002 (Section 2.2.2.1)	Schoen, Baker, Colby and To[188]	CUA	MSUD, MCADD, Glutaric Aciduria, MMA, PPA, Urea cycle disorders, Homocystinurea	MS/MS yields an ICER of $5,827/QALY
2002 (Section 2.2.2.2)	Insinga, Laessig and Hoffman[189]	CUA	MCADD and other fatty acid disorders	MS/MS yields a ICER of $6,008/QALY
2003 (Section 2.2.2.3)	Venditti, Venditti, Berry et al.[190]	CEA/CUA	MCADD	MS/MS screening for MCADD requires an additional $5,600/QALY ($11,000/LY) as compared to no screening. Costs offset in next 20 years.
2006 (Section 2.2.2.4)	Carroll & Downs[191]	CUA	PKU, CAH, CH, MSUD, Galactosemia, Homocystinuria, MCADD, biotinidase deficiency	Multi-test screening is dominant approach in all disorders except CAH and Galactosemia
2006 (Section 2.2.2.5)	Feuchtbaum & Cunningham[192]	CEA, CBA, CUA	Several	MS/MS screening saves $1.5 million annually. Screening is the dominant strategy in CBA and CUA
2007 (Section 2.2.2.6)	Tran, Banerjee, Li et al.[193]	CEA/CUA	MCADD	Screening for MCADD with MS/MS is cost-effective based on a threshold value of $20,000 per QALY

188 Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* Oct 2002;110(4):781-786.

189 Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Pediatr.* Oct 2002;141(4):524-531.

190 Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

191 Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Ibid.May 2006;117(5 Pt 2):S287-295.

192 Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Ibid.:S280-286.

193 Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, Dooley K. Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin Biochem.* Feb 2007;40(3-4):235-241.

2007 (Section 2.2.2.7)	Cipriano, Rupar, Zaric[194]	CEA	Several	Average cost of screening for PKU, along with 14 other disorders is $95,000 per life year gained.
Current Study	Tiwana	CUA	ASA and CIT, HCY, MSUD, Fatty Acid Disorders, tyrosinemia, GA I, Classical Organic Acid Disorders	Expanded screening with these disorders costs $12,000/QALY as compared to pre-expansion screening.

Results of the overall cost-effectiveness analysis are comparable with the results of other studies done in the past (Table 5.1). However, there are differences in the disease states included in these analyses. Other differences include varying costs and effectiveness estimates. For example, the base-case results of the current study show that the ICER for expanded screening was approximately $12,000/QALY (2007 dollars) at a discount rate of 3%. In their 2002 study, Schoen and colleagues reported their base-case estimate as $5,827/QALY (2002 dollars).[195] Their results were based on estimates of a number of disease states, including PKU. While the current study includes cost-effectiveness estimates of screening for 6 of the 7 disorder categories used by Schoen et al., it does not include cost and effectiveness analyses for PKU. Inclusion of PKU may have changed the results of the study since it is a much more prevalent condition as compared to many other disorders. The Schoen study also estimated that the treatment cost for MCADD is zero while in the current study, we included the cost of carnitine supplementation ($4,000 to $6,000 per year) as a treatment cost for those MCADD patients who had experienced one or more episodes of hypoglycemia.

In the Insinga study, it was reported that screening for MCADD and other fatty acids via tandem mass spectrometry (MS/MS) resulted in an ICER of $6,008/QALY.

194 Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

195 Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* Oct 2002;110(4):781-786.

They also included initial capital investment costs related to MS/MS. These costs were not included in the current study. Further, screening for multiple disorders may be more cost-effective as compared to screening for individual disorders.[196]

Study results are also comparable to the findings of Venditti et al. (2003) where the cost of screening for MCADD was estimated at $5,600/QALY (2001 US Dollars).[197] The ICER for MCADD screening as compared to no screening was estimated at approximately $3,000/QALY in our study at a discount rate of 3%. Although MCADD is deemed cost-effective by both the studies, there are some key differences in the costs included in the Venditti study and the current study. Our study includes only direct medical costs where as the Venditti study included a societal perspective which would also include indirect costs due to productivity losses. The base-case estimate for the annual cost of carnitine supplementation is also assumed to be zero for the screened patients. This again is divergent from the estimates used in the current study where a base-case estimate of $5,000 per year was used for carnitine supplementation for MCADD patients. The risk of mortality in the unscreened patients diagnosed clinically was also much higher (40% or higher) than the estimates we used (25%).

The Carroll and Downs study also compared a multi-test screening program with a "no screen" strategy and reported that screening was the dominant strategy for all disorders except congenital adrenal hyperplasia and galactosemia.[198] Most of the conditions included in their analysis were already being screened for during the pre-

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196 Insinga RP, Laessig RH, Hoffman GL. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Pediatr.* Oct 2002;141(4):524-531.

197 Venditti LN, Venditti CP, Berry GT, et al. Newborn screening by tandem mass spectrometry for medium-chain Acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics.* Nov 2003;112(5):1005-1015.

198 Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. Ibid.May 2006;117(5 Pt 2):S287-295.

expansion screening program in Texas. The current study includes only the newly added disorders to the screening panel. Of those, MSUD, MCADDD and HCY were also studied by Carroll and Downs. However, our study results show that screening for HCY is dominant while screening for the remaining disorder categories is cost-effective as compared to no screening. The Carroll and Downs study also utilized a multiplicative utility model where individual values of disutility were multiplied to account for multiple sequelae suffered by the same patient. In the present study, we used the utility value of the most debilitating condition versus using a product of individual utility values. For example, for a mentally retarded child on special diet, the utility value of mental retardation was used and not that of being on special diet. Carroll and Downs also used separate utility estimates for mild, moderate and severe cases of each disorder. Only average utility values were used in the current analysis.

The current study results of $12,000/QALY are also higher than the cost-effectiveness estimate provided by Feuchtbaum and Cunningham.[199] According to their estimates, screening cost $1,628/QALY (2006 US dollars) in the base-case estimate. Instead of allocating separate costs to each of the disease sequelae, they had used an average estimate of $1 million for the cost of life time treatment and follow-up. Their estimate was derived from a CDC report published in 2003. However, the report elaborates that most of the costs in this $1 million estimate were based on the productivity loss due to lost wages and early mortality.[200] The current study does not include productivity losses incurred either by the parents or by the patients (after they

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199 Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Ibid.:S280-286.

200 Honeycutt A, Grosse S, Dunlap L, et al. Economic costs of mental retardation, cerebral palsy, hearing loss, and vision impairment. *Research in Social Science and Disability.* 2003;3:207-228.

reach adulthood). If indirect costs were included in the present study, the results may be more comparable to the conclusions of Feuchtbaum and Cunningham.

Results of the current study show that screening for MCADD is cost-effective. This is in agreement with the findings of the Tran study (2007) where MCADD screening with MS/MS was reported as cost-effective at a threshold of C$20,000/QALY (USD15,400; 2004 estimate).[201] However, the estimates of mortality due to MCADD used in the Tran study were quite different from the ones used in our study. The literature shows that the likelihood of mortality is very small if timely screening and treatment is provided for MCADD. Therefore, we consider the the 6% probability for screened MCADD patients used by the Tran study to be an over estimation. Mortality for unscreened MCADD patients in the current study has been estimated at 20-25%.[202] The Tran study used a probability of 8% for such patients which may be an under estimation.

Study results also share some similarities with those of a recent study based on the cost-effectiveness of expanding newborn screening in Ontario Canada. Cipriano et al. (2007) reported that if MS/MS is used for screening newborns for PKU along with other metabolic disorders, it would only be cost-effective to include PKU and 14 other conditions on a combined newborn screening panel. Inclusion of MSUD, GA I, COAD and MCADD and other fatty acid disorders along with PKU would cost less than C$70,000 (USD 53,900; 2004 estimate) per life year gained.[203] The Cipriano et al. study also reports that the addition of each of the remaining disorders (including Tyrosinemia,

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201 Tran K, Banerjee S, Li H, Noorani HZ, Mensinkai S, Dooley K. Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin Biochem.* Feb 2007;40(3-4):235-241.

202 Grosse SD, Khoury MJ, Greene CL, Crider KS, Pollitt RJ. The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genet Med.* Apr 2006;8(4):205-212.

203 Cipriano LE, Rupar CA, Zaric GS. The cost-effectiveness of expanding newborn screening for up to 21 inherited metabolic disorders using tandem mass spectrometry: results from a decision-analytic model. *Value in Health.* Mar-Apr 2007;10(2):83-97.

HCY, ASA, CIT and two other disorders) would cost at least $300,000 (USD 231,000; 2004 estimate) per life year. These results are somewhat divergent from our findings. Our results do show that the ICER of screening for ASA and CIT is above the threshold of $50,000/QALY. However, our study found that screening for Tyrosinemia and HCY is cost-effective (dominant for HCY). It is important to point out some key methodological differences between the Cipriano et al. study and the current study. Their study was proposing the expansion of newborn screening in Ontario. Therefore, they included the disorders in a step-wise manner where the decision to include each successive disorder in the panel could be based on incidence, prevalence and the availability of effective treatment. While these are valid points to consider before any expansion of an existing program, they may not be useful for estimating the cost-effectiveness of an expansion that has already taken place. In our study, we looked at all the disorders simultaneously. So the incremental costs and effectiveness compare the program before and after simultaneous expansion. If Texas decided to undertake the inclusion of one or more disorders in the future, the approach used by Cipriano et al. may be helpful in the decision making process. Another difference is the use of life years as the denominator in their cost-effectiveness analysis. We used quality adjusted life years where the utility of being in each of the states was accounted for by using estimates available from the literature.

5.8 Results of Sensitivity Analyses

Results of the one-way sensitivity analyses point to several variables that may impact the results of the cost-effectiveness analysis. The discount rate impacts all the costs and all the utilities as well; therefore, study results are sensitive to changes in the discount rate.

Cost of Tyrosinemia medications, cost of special diet and cost of carnitine supplementation were some of the most influential variables in the cost category. Since the 1990s, all infants detected with Tyrosinemia are treated with expensive NTBC therapy. Cost of this therapy can potentially impact the results of the cost-effectiveness analysis. Every child who tests positive for any of the disorders is placed on a special diet. Therefore, special diet cost has an impact on the entire cohort included in the analysis. Cost of carnitine supplementation is also an important variable in the cost category. Carnitine diet is recommended for all children who have complications related to MCADD. Of all the disorders included in the study, MCADD and other fatty acid disorders is the most prevalent group of conditions and therefore cost of carnitine can affect a significant number of patients each year. Cost of neurological damage can also have a widespread impact on the study results since it is a possible outcome for many disorders included in this study. Some other variables such as the cost of liver transplant did not seem to influence the study results. Although the cost of liver transplant is very high, it only impacts a very small proportion of the study cohort.

Within the probability category, a significant decline in the probability of death is seen for the screened versus unscreened populations. Further, a decline in mortality is the only major difference between the screened and the unscreened patients and other sequelae do not differ in spite of screening. Patients who die due to ASA and CIT will not incur any direct medical costs, neither will they have any utilities (since the utility value of being dead is zero). This may explain the influence of probability of death for ASA and CIT as an influential variable in this category. Patients with GA I have a very high risk of neurological damage without screening and the risk still stays significant in the screened patients. These patients would incur significant costs because of these outcomes which may explain why the probability of neurological damage in all cases of

GA I ranks as a significant variable. The probability of being diagnosed with Tyrosinemia is directly related to the yearly treatment costs of these patients. If more patients are diagnosed with Tyrosinemia, treatment costs would automatically go up

For the category of utility values used in the Markov model, utility of being on treatment (with special diet) without any additional complications impacts most of the members of the cohort. Therefore, it is not surprising that this variable shows as the most influential variable in the tornado diagram for the utility values.

5.9 STUDY LIMITATIONS

The main limitation of this study is that estimates from the literature were used instead of actual data for most of the costs, probabilities and outcomes. Each of the published studies have their own inherent limitations and the screening program described in a study may be systematically different from the newborn screening program of Texas. Many of the published results are also based on relatively short-term follow-up. For example, the hospitalization data for MCADD patients in Australia was only reported for the first four years of life.[204] We estimated the likelihood of hospitalization for children older than 4 years of age. Further, some of the studies have been conducted in specialty clinics or in high incidence communities. Results from such studies may not be generalizable to other health care facilities or to communities where many of the disorders are extremely rare. Expert opinion was used for some of the sequelae, where data from the literature were unclear or insufficient. There may be some subjectivity in expert opinion.

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[204] Haas M, Chaplin M, Joy P, Wiley V, Black C, Wilcken B. Healthcare use and costs of medium-chain acyl-CoA dehydrogenase deficiency in Australia: screening versus no screening. *J Pediatr.* Aug 2007;151(2):121-126, 126 e121.

Although sensitivity analyses showed that study results were robust to a wide range in variables, it is still important to recognize that the clinical data and the economic estimates included in this study came from different sources in the literature. For example, clinical data for MSUD and GA I were obtained from studies conducted in Pennsylvania and cost estimates for many variables were obtained from studies conducted in California and Canada. Data from such varied sources may not be generalizable to Texas.

Based on the newborn screening program, specimens may be drawn from infants between 24-72 hours of birth. Screening results are usually available 5-10 days from birth. Some infants may die before any concrete diagnosis can be made.

It is important to recognize that due to screening, milder forms of the disease may also be detected. Due to the mild nature of the underlying disease, outcomes for these patients will be inherently better than those who have the severe form of the same disorder. Inclusion of mildly affected patients in the cohort may create a positive bias in favor of screening. On the other hand, when data on unscreened cohorts is used, it includes only the more severe cases since the mild forms of the disease may go undiagnosed. Their disease prognosis is worse because of the severity of their disease which confounds the effect of late treatment (as compared to that of screened cohorts who are likely to receive early treatment).

Another limitation was the lack of utility estimates specific to newborn screening disorders. Although there is literature on conditions like mental retardation, neurological damage and renal failure, it is problematic to account for the disutility caused by individual sequelae when a patient is experiencing more than one complication. Further, use of published estimates may not adequately reflect the disutility experienced by the pediatric patient. There have been comparisons of the disutility caused by a false positive

newborn screen result with that of a false positive cancer screen. It may be argued that the disutility of a false positive cancer screen often pertains to the patient (except in pediatric patients) whereas most of the emotional trauma of a false positive newborn screen is experienced by the infant's family.

5.10 Significance of This Study

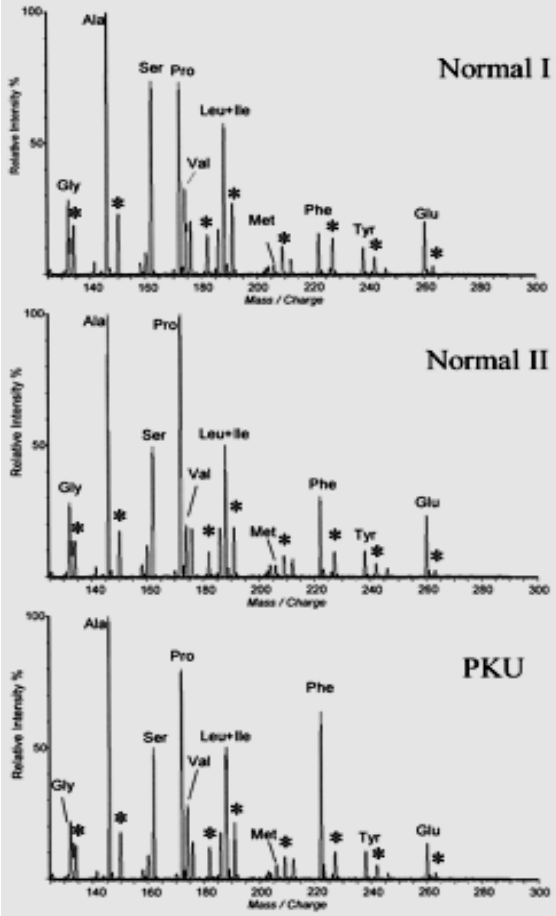
Since the expansion of its screening panel in 2007, this is the first study to estimate the cost-effectiveness of the newborn screening program in Texas. Further expansions of the program are also imminent. Results of the present study capture a variety of aspects related to newborn screening in Texas. Cost estimates for laboratory activities (screening test) and case management activities (follow-up and treatment of positive cases) are included in this study. The study methodology provides a compilation of disease prognosis and outcomes data (based on severity) obtained from a number of recent studies. Study results may further substantiate the policy decision of expanding newborn screening in Texas. Estimates of long-term costs may be useful in future plans regarding patient care. So far, most of the focus of newborn screening in general is to provide short term diagnosis and care. This study also highlights some of the existing gaps in the clinical, economic, and quality of life data related to newborn screening. An increased awareness of these gaps in knowledge may stimulate additional research in these areas.

5.11 Future Research

Newborn screening is an extremely diverse research area with implications in clinical research, health technology assessment, outcomes research, health policy, ethics and law. Findings of the current study help in answering some of the questions related to the economic viability of the decision to expand newborn screening panel in Texas with

possible applications for the rest of the country as well. At the same time, it also points to some major gaps in this important field of research. Lack of good quality studies in health related quality of life in pediatric patients diagnosed with metabolic disorders is a case in point. Economic impact of upcoming newborn screening expansions, their policy implications, and program evaluation of the current newborn screening program are all pertinent areas for future research.

Appendix A Example MS/MS Profile



MS/MS amino acid profiles from neonatal specimens that tested as initial negative (Normal I, top panel), false positive (Normal II, middle panel), and confirmed PKU-positive (bottom panel) in initial fluorometry tests. Source: Chace DH, Sherwin JE, Hillamn SL, Lorey F, Cunningham GC. Use of phenylalanine to tyrosine ratio determined by tandem mass spectrometry to improve newborn screening for phenylketonuria of early discharge specimens collected during the first 24 hours. *Clinical Chemistry* 1998; 44:2405-9.

Appendix B National Newborn Screening Status Report

Updated 05/04/09

The U.S. National Screening Status Report lists the status of newborn screening in the United States.

Dot "●" indicates that screening for the condition is universally required by Law or Rule and fully implemented
A = universally offered but not yet required, **B** = offered to select populations, or by request, **C** = testing required but not yet implemented
D = likely to be detected (and reported) as a by-product of MRM screening (MS/MS) targeted by Law or Rule

STATE	Core[1] Conditions									Additional Conditions Included in Screening Panel (universally required unless otherwise indicated)
	Hearing	Endocrine		Hemoglobin			Other			
	HEAR	CH	CAH	Hb S/S	Hb S/A	Hb S/C	BIO	GALT	CF	
Alabama	●	●	●	●	●	●	●	●	●	
Alaska	●	●	●	●	●	●	●	●	●	
Arizona	A	●	●	●	●	●	●	●	●	
Arkansas	●	●	●	●	●	●	●	●	●	
California	B	●	●	●	●	●	●	●	●	HHH; PRO; EMA
Colorado	●	●	●	●	●	●	●	●	●	
Connecticut	●	●	●	●	●	●	●	●	B	HHH; HIV[2]; NKH
D.C.	●	●	●	●	●	●	●	●	●	G6PD
Delaware	●	●	●	●	●	●	●	●	●	
Florida	●	●	●	●	●	●	●	●	●	
Georgia	A	●	●	●	●	●	●	●	●	
Hawaii	●	●	●	●	●	●	●	●	●	
Idaho	A	●	●	●	●	●	●	●	●	
Illinois	●	●	●	●	●	●	●	●	●	NKH, 5-OXO, HIV[2]
Indiana	●	●	●	●	●	●	●	●	●	
Iowa	●	●	●	●	●	●	●	●	●	
Kansas	●	●	●	●	●	●	●	●	●	
Kentucky	A	●	●	●	●	●	●	●	●	
Louisiana	●	●	●	●	●	●	●	●	●	
Maine	A	●	●	●	●	●	●	●	●	HHH; CPS (D)
Maryland	●	●	●	●	●	●	●	●	●	EMA
Massachusetts	●	●	●	●	●	●	●	●	●	TOXO; HHH, SCID (A); CPS (D)
Michigan	●	●	●	●	●	●	●	●	●	
Minnesota	●	●	●	●	●	●	●	●	●	
Mississippi	●	●	●	●	●	●	●	●	●	5-OXO; CPS; HHH
Missouri	●	●	●	●	●	●	●	●	●	
Montana	●	●	●	●	●	●	●	●	●	
Nebraska	A	●	●	●	●	●	●	●	●	5-OXO; HHH; NKH (A)
Nevada	A	●	●	●	●	●	●	●	●	
New Hampshire	A	●	●	●	●	●	●	●	●	TOXO
New Jersey	●	●	●	●	●	●	●	●	●	
New Mexico	●	●	●	●	●	●	●	●	●	
New York	●	●	●	●	●	●	●	●	●	HIV; HHH; Krabbe Disease
North Carolina	●	●	●	●	●	●	●	●	●	
North Dakota	A	●	●	●	●	●	●	●	●	HHH; NKH
Ohio	●	●	●	●	●	●	●	●	●	
Oklahoma	●	●	●	●	●	●	C	●	●	
Oregon	A	●	●	●	●	●	●	●	●	
Pennsylvania	●	●	●	●	●	●	C	●	C	5-OXO; CPS; G6PD; HHH; NKH (B)
Rhode Island	●	●	●	●	●	●	●	●	●	
South Carolina	●	●	●	●	●	●	●	●	●	
South Dakota	A	●	●	●	●	●	●	●	●	5-OXO; EMA; HHH; NKH
Tennessee	●	●	●	●	●	●	●	●	●	HHH; NKH
Texas	B	●	●	●	●	●	●	●	C	
Utah	●	●	●	●	●	●	●	●	●	
Vermont	●	●	●	●	●	●	●	●	●	
Virginia	●	●	●	●	●	●	●	●	●	
Washington	A	●	●	●	●	●	●	●	●	
West Virginia	●	●	●	●	●	●	●	●	●	
Wisconsin	A	●	●	●	●	●	●	●	●	SCID
Wyoming	●	●	●	●	●	●	●	●	●	

[1]Terminology consistent with ACMG report - Newborn Screening: Towards a Uniform Screening Panel and System. Genet Med. 2006; 8(5) Suppl: S12-S252
[2]Newborn screened for HIV only if mother was not screened during pregnancy

Additional Conditions/Abbreviations and Names

BIO	Biotinidase	**CF**	Cystic fibrosis	**GALT**	Transferase deficient galactosemia (Classical)	**HB S/C**	Sickle – C disease	**HEAR**	Hearing screening
CAH	Congenital adrenal hyperplasia	**CH**	Congenital hypothyroidism	**HB S/S**	Sickle cell anemia	**HB S/A**	S-βeta thalassemia		

Other Disorders

5-OXO	5-oxoprolinuria (pyroglutamic aciduria)	**G6PD**	Glucose 6 phosphate dehydrogenase	**NKH**	Nonketotic hyperglycinemia
CPS	Carbamoylphosphate synthetase	**HHH**	Hyperammonemia/ornithinemia/ citrullinemia (Ornithine transporter defect)	**PRO**	Prolinemia
EMA	Ethylmalonic encephalopathy	**HIV**	Human immunodeficiency virus	**TOXO**	Toxoplasmosis

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hat screening for the condition is universally required by Law or Rule and fully implemented

A = universally offered but not yet required, **B** = offered to select populations, or by request, **C** = testing required but not yet implemented

D = likely to be detected (and reported) as a by-product of MRM screening (MS/MS) targeted by Law or Rule

STATE	Core[1] Conditions - Metabolic																		
	Fatty Acid Disorders					Organic Acid Disorders									Amino Acid Disorders				
	CUD	LCHAD	MCAD	TFP	VLCAD	GA-I	HMG	IVA	3-MCC	Cbl-A,B	BKT	MUT	PROP	MCD	ASA	CIT	HCY	MSUD	PKU	TYR- I
Alabama	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Alaska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arizona	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arkansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
California	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Colorado	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Connecticut	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
D. of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Delaware	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Florida	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	D
Georgia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hawaii	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Idaho	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Illinois	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Iowa	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kentucky	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Louisiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maryland	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Massachusetts	●	●	●	D	●	●	●	●	D	●	●	●	●	D	●	●	●	●	●	●
Michigan	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Missouri	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Montana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nebraska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nevada	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Hampshire	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
New Jersey	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Mexico	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
North Carolina		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
North Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Ohio	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Oklahoma	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oregon	D	●	●	D	●	●	●	●	●	D	D	●	●	D	●	●	●	●	●	●
Pennsylvania	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	●	●	C
Rhode Island	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tennessee	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Texas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Utah	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vermont	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Washington	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	●	●	●	●	●
West Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Wisconsin	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Wyoming	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

[1]Terminology consistent with ACMG report - Newborn Screening: Towards a Uniform Screening Panel and System. Genet Med. 2006; 8(5) Suppl: S12-S252

Deficiency/Disorder Abbreviations and Names (optional nomenclature)

3-MCC	3-Methylcrotonyl-CoA carboxylase	**CUD**	Carnitine uptake defect	**LCHAD**	Long-chain L-3- hydroxyacyl-	**PKU**	Phenylketonuria/

			(Carnitine transport defect)		CoA dehydrogenase		hyperphenylalaninemia
ASA	Argininosuccinate aciduria	**GA-1**	Glutaric acidemia type 1	**MCAD**	Medium-chain acyl-CoA dehydrogenase	**PROP**	Propionic acidemia (Propionyl-CoA carboxylase)
BKT	Beta ketothiolase (mitochondrial acetoacetyl-CoA thiolase ; short-chain ketoacyl thiolase; T2)	**HCY**	Homocystinuria (cystathionine beta synthase)	**MCD**	Multiple carboxylase (Holocarboxylase synthetase)	**TFP**	Trifunctional protein deficiency
CBL A,B	Methylmalonic acidemia (Vitamin B12 Disorders)	**HMG**	3-Hydroxy 3 - methylglutaric aciduria (3-Hydroxy 3-methylglutaryl-CoA lyase)	**MSUD**	Maple syrup urine disease (branched-chain ketoacid dehydrogenase)	**TYR-1**	Tyrosinemia Type 1
CIT I	Citrullinemia type I (Argininosuccinate synthetase)	**IVA**	Isovaleric acidemia (Isovaleryl-CoA dehydrogenase)	**MUT**	Methylmalonic Acidemia (methylmalonyl-CoA mutase)	**VLCAD**	Very long-chain acyl-CoA dehydrogenase

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● indicates that screening for the condition is universally required by Law or Rule and fully implemented

A = universally offered but not yet required, **B** = offered to select populations, or by request, **C** = testing required but not yet implemented

D = likely to be detected (and reported) as a by-product of MRM screening (MS/MS) targeted by Law or Rule

STATE	Secondary Target [1] Conditions																							
	Fatty Acid Disorders								Organic Acid Disorders						Amino Acid Disorders								Other Metabolic		Hbg
	CACT	CPT-Ia	CPT- II	DE-RED.	GA-II	MCKAT	M/SCHAD	SC AD	2M3HBA	2MBG	3MGA	Cbl-C,D	IBG	MAL	ARG	BIOPT-BS	BIOPT-RG	CIT-II	H-PHE	MET	TYR- II	TYR- III	GALE	GALK	Variant Hbg's
Alabama	●		●		●				●	●	●	●				D	D	●	●	●	●	●			D
Alaska	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Arizona	D	D	D		D				D		D	D						D	D		D	D			D
Arkansas																			●						●
California	●	●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●				●
Colorado	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●			●
Connecticut	●	●	●	●	●			●				●		●	●			●	●	●	●	●	●	●	●
D. of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	A	A	●	●	●	●	●	●	●	●
Delaware	●		●		●	D		●	D	●	D	●	●		●	D	D	●	●	●	●	●	●	●	●
Florida	●	●	●		●			●											●		●				
Georgia	●	D	●		●	D	●	D	●	D	●	●	D	D	A				●	●	●	●	B	B	●
Hawaii	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Idaho	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Illinois	●	D	●	D	●	D	●	●	D	●	●	●	●	●	●	D	D	D	●	●	●	●	●	●	●
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Iowa	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Kansas																			●						●
Kentucky	A	A	A		A			●	A	A	A	A	A	A	A	D	D	A	●	A	A	A			●
Louisiana																			●						●
Maine	D	D	●		●			●		D	D	●	D		●			●	●	D	●	D	●	●	●
Maryland	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	B	B	●	●	●	●	●	●	●	●
Massachusetts	D	D	A	A	D	D	A	D	D	D	D	●	D	A	●	D	D	A	D	D	D	D	D	D	●
Michigan	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●					●
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	A	●	A	●	●	A	●	●	●	●	●	●	A	A	●	●	●	●	A	●	●	●
Missouri	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Montana	D		D	D	D	D	D	D	D	D	D	D	D	D		D	D	D	●	D	D	D			●
Nebraska	A		A		A			A		A		A	A	A	A			A	●	A	A		●	●	●
Nevada	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	A
New Hampshire	D	D	●		●					D	D	D			●	D	D	D	●	D			●	●	●
New Jersey	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Mexico	A	D	A		A			A	D	D	A	A	D	D	D	B	B	A	A	A	A	D	B	B	●
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●			●
North Carolina	●		●		●			●		●		●	●			●	●	●	●	●	●	●			●
North Dakota	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Ohio	●	●	●		●			●		●		●	●		●			●	●	●					●
Oklahoma	●	●	●		●	D		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Oregon	●	D	●		●			●	D	D	●	●	D	D	D	B	B	●	●	●	●	D	B	B	●
Pennsylvania	B	B	B	B	B		B	B		B	B	B	B	B	B	B	B	B	●	B	B	B	●	●	●
Rhode Island		D																	●				●	●	●
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●
South Dakota	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●
Tennessee	●	●	●	●	●	D		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Texas	D	D	D		D				D	D	D	D				D	D	D	●	D	D	D			●
Utah	●	●	●		●	D		●	●	●	D	●	●	D	●	●	●	●	●	●	●	●			●
Vermont	D	D	D		D					D	D	●			D			●	●	D	D	D	●	●	●
Virginia	D	D	D	D	D	D	D	D	D	D	D	D	D		D	D	D	D	●	D	D	D	D	D	●
Washington	D		D		D	D			D	D	D	D				D	D	●	D	D					●
West Virginia	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	●	D	D	D	●	●	●
Wisconsin	●		●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●	●	●			●
Wyoming	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A			A	●	A	A	B			●

[1]Terminology consistent with ACMG report - Newborn Screening: Towards a Uniform Screening Panel and System. Genet Med. 2006; 8(5) Suppl: S12-S252

Deficiency/Disorder Abbreviations and Names (optional nomenclature)

2M3HBA	2-Methyl-3-hydroxy butyric aciduria	**CACT**	Carnitine acylcarnitine translocase	**GA-II**	Glutaric acidemia Type II	**MAL**	Malonic acidemia (Malonyl-CoA decarboxylase)
2MBG	2-Methylbutyryl-CoA dehydrogenase	**CBL-C,D**	Methylmalonic acidemia (Cbl C,D)	**GALE**	Galactose epimerase	**MCKAT**	Medium-chain ketoacyl-CoA thiolase
3MGA	3-Methylglutaconic aciduria	**CIT-II**	Citrullinemia type II	**GALK**	Galactokinase	**MET**	Hypermethioninemia
ARG	Argininemia (Arginase deficiency)	**CPT-Ia**	Carnitine palmitoyltransferase I	**H-PHE**	Benign hyperphenylalaninemia	**SCAD**	Short-chain acyl-CoA dehydrogenase
BIOPT-BS	Defects of biopterin cofactor biosynthesis	**CPT-II**	Carnitine palmitoyltransferase II	**IBG**	Isobutyryl-CoA dehydrogenase	**TYR-II**	Tyrosinemia type II
BIOPT-REG	Defects of biopterin cofactor regeneration	**De-Red**	Dienoyl-CoA reductase	**M/SCHAD**	Medium/Short chain L-3-hydroxy acyl-CoA dehydrogenase	**TYR-III**	Tyrosinemia type III

Appendix C Fee Schedule by State

Trends in Newborn Screening Fees Per Infant

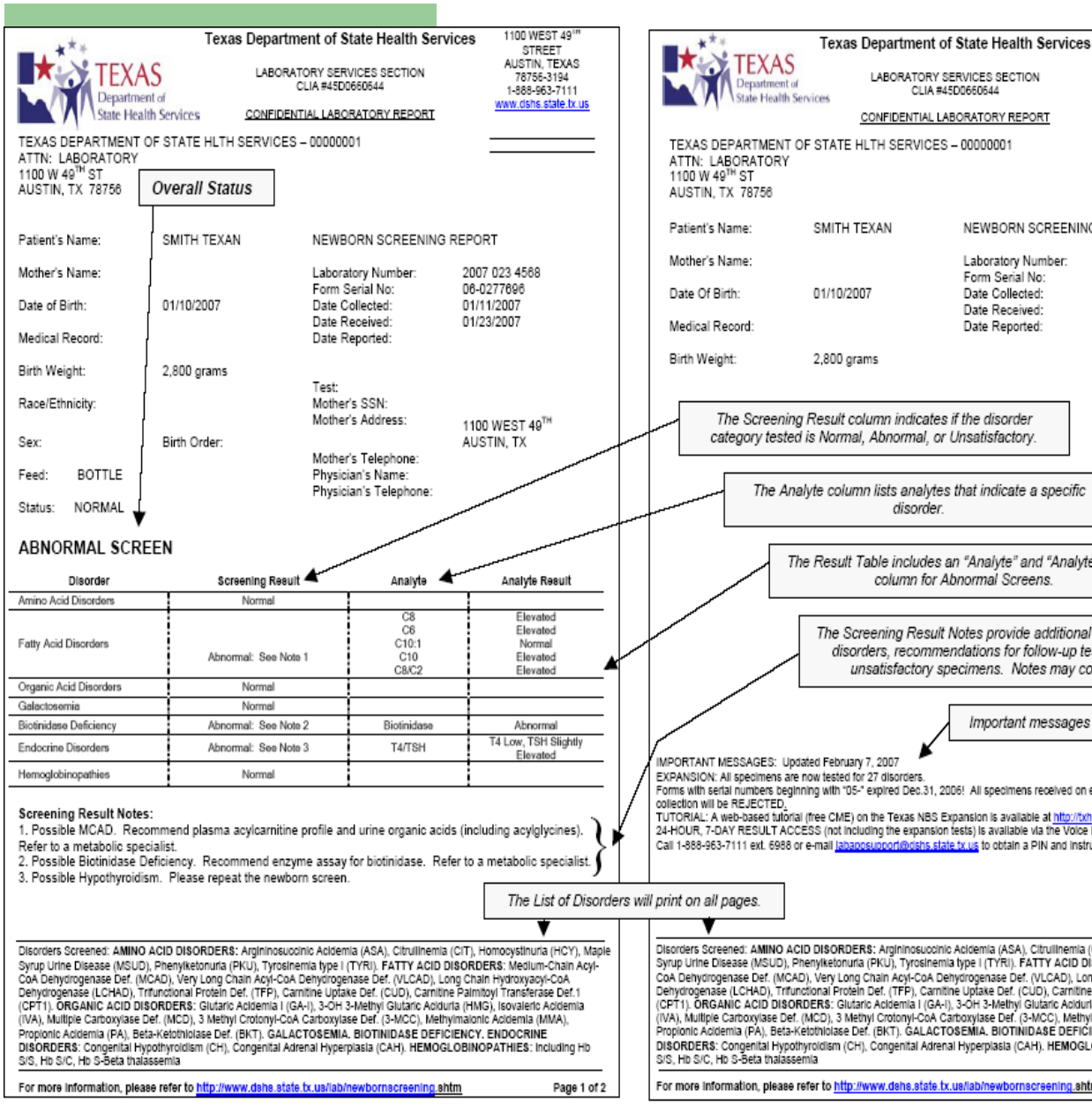
State	1996	1997	1998	1999	2000	2002	2004
Alabama	NA	$24.00	$24.00	$24.00	$24.00	$34.00	$139.33
Alaska	$24.00	$24.00	$24.00	$24.00	$24.00	$24.00	$55.00
Arizona	$20.00	$20.00	$20.00	$20.00	$20.00	$20.00	$20.00
Arkansas	$14.83	$14.83	$14.83	$14.83	$14.83	$14.83	$14.83
California	$42.00	$42.00	$42.00	$42.00	$42.00	$60.00	$60.00
Colorado	$33.50	$33.50	$33.50	$33.50	$33.50	$43.37	$53.25
Connecticut	$18.00	$18.00	$18.00	$18.00	$18.00	$28.00	$28.00
Delaware	$40.69	$40.69	$40.69	$40.69	$40.69	$40.69	$64.00
District of Columbia	No fee	No fee	No fee	No fee	No fee	No fee	No fee
Florida	$20.00	$20.00	$20.00	$20.00	$20.00	$20.00	$15.00
Georgia	No fee	No fee	No fee	No fee	No fee	No fee	No fee
Hawaii	No fee	$4.00	$27.00	$27.00	$27.00	$27.00	$47.00
Idaho	No fee	No fee	No fee	No fee	No fee	$18.00	$23.00
Illinois	$25.00	$25.00	$32.00	$32.00	$32.00	$32.00	$47.00
Indiana	$22.10	$22.10	$22.10	$22.10	$28.50	$39.50	$39.50
Iowa	$28.00	$30.00	$30.00	$30.00	$33.00	$46.00	$56.00
Kansas	No fee	No fee	No fee	No fee	No fee	No fee	No fee
Kentucky	NA	$14.50	$14.50	$14.50	$14.50	$14.50	$14.50
Louisiana	$12.00	$12.00	$12.00	$18.00	$18.00	$18.00	$40.00
Maine	$18.00	$18.00	$18.00	$26.75	$26.75	$33.00	$44.00
Maryland	$15.75	$15.75	$15.75	$15.75	$15.75	$30.00	$42.00
Massachusetts	$42.00	$42.00	$42.00	$49.55	$49.55	$49.55	$54.75
Michigan	$28.02	$28.02	$28.58	$29.38	$39.00	$42.61	$54.84
Minnesota	$13.00	$13.00	$21.00	$21.00	$21.00	$21.00	$61.00
Mississippi	$20.00	$20.00	$20.00	$20.00	$35.00	$25.00	$70.00
Missouri	$25.00	$15.00	$15.00	$13.00	$13.00	$25.00	$25.00
Montana	$15.00	$15.00	$18.50	$35.50	$36.92	$36.92	$39.34
Nebraska	NA	No fee	$54.60	$54.60	$54.60	$54.60	$64.00
Nevada	NA	$30.00	$30.00	$30.00	$30.00	$30.00	$30.75
New Hampshire	NA	$12.50	$12.50	$12.50	$18.00	$18.00	$18.00

New Jersey	$27.00	$27.00	$27.00	$34.00	$34.00	$34.00	$71.00
New Mexico	$20.00	$20.00	$20.00	$20.00	$20.00	$32.00	$32.00
New York	No fee	No fee	No fee	No fee	No fee	No fee	No fee
North Carolina	No fee	No fee	No fee	No fee	No fee	$10.00	$10.00
North Dakota	$15.00	$15.00	$15.00	$16.00	$17.00	$18.00	$36.00
Ohio	$27.00	$27.00	$27.00	$27.50	$27.00	$33.75	$33.75
Oklahoma	$10.50	$10.50	$10.50	$10.50	$10.50	$10.50	$75.59
Oregon	$28.00	$28.00	$32.00	$32.00	$32.00	$54.00	$54.00
Pennsylvania	$18.50	$12.00	$18.50	No fee	No fee	No fee	No fee
Rhode Island	$59.00	$59.00	$59.00	$55.00	$59.00	$59.00	$59.00
South Carolina	$21.00	$21.00	$21.00	$21.00	$21.00	$21.00	$42.00
South Dakota	No fee	No fee	No fee	No fee	No fee	No fee	$16.20
Tennessee	$10.00	$10.00	$10.00	$10.00	$17.50	$17.50	$47.50
Texas	No fee	No fee	$13.75	$13.75	$13.75	$19.50	$19.50
Utah	$21.00	$21.00	$27.50	$27.50	$27.00	$31.00	$31.00
Vermont	$21.00	$21.00	$21.00	$27.00	$27.00	$27.00	$33.30
Virginia	$16.00	$16.00	$16.00	$16.00	$16.00	$27.00	$32.00
Washington	$39.90	$33.80	$35.75	$35.75	$39.25	$40.40	$60.90
West Virginia	No fee	No fee	$15.85	$12.64	$20.46	No fee	No fee
Wisconsin	$43.25	$44.00	$45.50	$55.50	$55.50	$59.50	$65.50
Wyoming	$12.25	$12.25	No fee	No fee	No fee	No fee	$45.00

Source: Johnson K, Lloyd-Puryear MA, Mann MY, Ramos LR, Therrell BL. Financing state newborn screening programs: sources and uses of funds. *Pediatrics*. May 2006;117(5 Pt 2):S270-279.

Appendix D Example Newborn Screening Specimen Collection Form

Appendix E Abnormal Screen Result



Texas Department of State Health Services

1100 WEST 49TH STREET
AUSTIN, TEXAS
78756-3194
1-888-963-7111
www.dshs.state.tx.us

LABORATORY SERVICES SECTION
CLIA #45D0660644

CONFIDENTIAL LABORATORY REPORT

TEXAS DEPARTMENT OF STATE HLTH SERVICES – 00000001
ATTN: LABORATORY
1100 W 49TH ST
AUSTIN, TX 78756

Overall Status

Patient's Name:	SMITH TEXAN	NEWBORN SCREENING REPORT	
Mother's Name:		Laboratory Number:	2007 023 4568
		Form Serial No:	06-0277696
Date of Birth:	01/10/2007	Date Collected:	01/11/2007
		Date Received:	01/23/2007
Medical Record:		Date Reported:	
Birth Weight:	2,800 grams		
		Test:	
Race/Ethnicity:		Mother's SSN:	
		Mother's Address:	1100 WEST 49TH
Sex:	Birth Order:		AUSTIN, TX
		Mother's Telephone:	
Feed: BOTTLE		Physician's Name:	
		Physician's Telephone:	
Status: NORMAL			

The Screening Result column indicates if the disorder category tested is Normal, Abnormal, or Unsatisfactory.

The Analyte column lists analytes that indicate a specific disorder.

The Result Table includes an "Analyte" and "Analyte column for Abnormal Screens.

The Screening Result Notes provide additional disorders, recommendations for follow-up te unsatisfactory specimens. Notes may co

Important messages

ABNORMAL SCREEN

Disorder	Screening Result	Analyte	Analyte Result
Amino Acid Disorders	Normal		
Fatty Acid Disorders	Abnormal: See Note 1	C8 C6 C10:1 C10 C8/C2	Elevated Elevated Normal Elevated Elevated
Organic Acid Disorders	Normal		
Galactosemia	Normal		
Biotinidase Deficiency	Abnormal: See Note 2	Biotinidase	Abnormal
Endocrine Disorders	Abnormal: See Note 3	T4/TSH	T4 Low, TSH Slightly Elevated
Hemoglobinopathies	Normal		

Screening Result Notes:
1. Possible MCAD. Recommend plasma acylcarnitine profile and urine organic acids (including acylglycines). Refer to a metabolic specialist.
2. Possible Biotinidase Deficiency. Recommend enzyme assay for biotinidase. Refer to a metabolic specialist.
3. Possible Hypothyroidism. Please repeat the newborn screen.

IMPORTANT MESSAGES: Updated February 7, 2007
EXPANSION: All specimens are now tested for 27 disorders.
Forms with serial numbers beginning with "05-" expired Dec.31, 2006! All specimens received on e collection will be REJECTED.
TUTORIAL: A web-based tutorial (free CME) on the Texas NBS Expansion is available at http://txh
24-HOUR, 7-DAY RESULT ACCESS (not including the expansion tests) is available via the Voice I Call 1-888-963-7111 ext. 6988 or e-mail labaccsupport@dshs.state.tx.us to obtain a PIN and instru

The List of Disorders will print on all pages.

Disorders Screened: **AMINO ACID DISORDERS:** Argininosuccinic Acidemia (ASA), Citrullinemia (CIT), Homocystinuria (HCY), Maple Syrup Urine Disease (MSUD), Phenylketonuria (PKU), Tyrosinemia type I (TYRI). **FATTY ACID DISORDERS:** Medium-Chain Acyl-CoA Dehydrogenase Def. (MCAD), Very Long Chain Acyl-CoA Dehydrogenase Def. (VLCAD), Long Chain Hydroxyacyl-CoA Dehydrogenase (LCHAD), Trifunctional Protein Def. (TFP), Carnitine Uptake Def. (CUD), Carnitine Palmitoyl Transferase Def.1 (CPT1). **ORGANIC ACID DISORDERS:** Glutaric Acidemia I (GA-I), 3-OH 3-Methyl Glutaric Aciduria (HMG), Isovaleric Acidemia (IVA), Multiple Carboxylase Def. (MCD), 3 Methyl Crotonyl-CoA Carboxylase Def. (3-MCC), Methylmalonic Acidemia (MMA), Propionic Acidemia (PA), Beta-Ketothiolase Def. (BKT). **GALACTOSEMIA. BIOTINIDASE DEFICIENCY. ENDOCRINE DISORDERS:** Congenital Hypothyroidism (CH), Congenital Adrenal Hyperplasia (CAH). **HEMOGLOBINOPATHIES:** Including Hb S/S, Hb S/C, Hb S-Beta thalassemia

For more information, please refer to http://www.dshs.state.tx.us/lab/newbornscreening.shtm

Page 1 of 2

Appendix F Fact Sheet Galactosemia (GALT)

What is GALT?

GALT is a rare, inherited problem. It is caused when the body can't break down galactose. Galactose is a sugar found in milk and milk products.

What Causes GALT?

Breast milk and most infant formulas have a sugar called lactose. The body breaks lactose down into sugars called glucose and galactose. Galactose must be broken down more before the body can use it for energy. An enzyme called galactose-1-phosphate uridyl transferase helps do this. Enzymes help start chemical reactions in the body. Most people with GALT don't have this special enzyme. This causes galactose to build up in the body.

What Symptoms or Problems Occur with GALT?

[Symptoms are something out of the ordinary that a parent notices.]

High levels of galactose poison the body and cause these serious problems:

- swollen liver
- kidney failure
- stunted growth and mental retardation
- cataracts in the eyes

Children and young adults treated for GALT may still have problems over the years with:

- speech
- language
- hearing
- clumsiness with hands
- bleeding in the gel-like part of the eye
- tremors (shaking)
- stunted growth
- learning disabilities

What is the Treatment for GALT?

Special Diet – The treatment for GALT is to limit galactose and lactose from the diet for life. All milk and all foods that have milk in them must not be used at all. This includes any kind of milk, such as cow's milk, goat's milk, and human breast milk. Your child should also not eat dairy products like butter, cheese, and yogurt. Other foods with small amounts of milk products must also not be eaten. These include foods with whey, casein, and curds.

Things to Remember

Children with GALT should be in the care of a doctor who specializes in the treatment of GALT. You will also have a dietitian who will teach you about special diets for your child. Dietitians know what are the right foods to eat.

Read labels carefully when you shop for your child's food. Many prepared foods have hidden ingredients that contain galactose.

Many medicines contain fillers that include galactose. It is important to ask the doctor and pharmacist about this for any medicines prescribed for your child.

Appendix G Act Sheet: Galactosemia

Appendix G Act Sheet: Galactosemia

Disclaimer: This information is adapted from American College of Medical Genetics website ACT sheets. http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm 10/06

Absent/Reduced Galactose-1-phosphate Uridyltransferase (GALT)
Classical Galactosemia

Differential Diagnosis: Galactosemia (galactose-1-phosphate uridyltransferase deficiency); GALT heterozygotes; GALT variants; artifactual reductions due to enzyme inactivation by high temperature and/or humidity.

Condition Description: In galactosemia, GALT deficiency results in accumulation of galactose-1-phosphate (Gal-1-P), and galactose, causing multiorgan disease.

Medical Emergency: ***Take the Following Immediate Actions***

- Contact family to inform them of the newborn screening result, ascertain clinical status, arrange immediate clinical evaluation, stop breast or cow's milk, and initiate non-lactose feeding (powder-based soy formula).
- Consult with metabolic specialist; refer if considered appropriate.
- Evaluate the infant (jaundice, poor feeding, vomiting, lethargy, bulging fontanel, and bleeding), and arrange diagnostic testing as directed by metabolic specialist.
- Initiate emergency treatment as recommended by metabolic specialist. If baby is sick, admit to hospital.
- Repeat newborn screen if second screen has not yet been done.
- Educate family about importance of diet change.
- Report findings to newborn screening program.

Confirmation of Diagnosis:
Quantification of erythrocyte galactose-1-phosphate (gal-1-P) and GALT.
Classical galactosemia shows <1% GALT activity and markedly increased gal-1-P.
Transfusions in infant can invalidate the results of erythrocyte enzyme assays. Enzyme variants may be distinguished by GALT electrophoresis or mutation analysis.
Clinical Considerations: Classical galactosemia presents in the first few days of life and may be fatal without treatment. Signs include poor feeding, vomiting, jaundice and, sometimes, lethargy and/or bleeding. Neonatal E. coli sepsis can occur and is often FATAL. Treatment is withdrawal of milk and, if symptomatic, emergency measures.

Additional Information:

New England Metabolic Consortium
http://www.childrenshospital.org/newenglandconsortium/NBS/gal/gal_protocol.htm

Gene Tests/Gene Clinics

Appendix H

TABLE H.1 ASA AND CIT: PROBABILITY OF DEATH WITH NO SCREEN

Cycle	Low	Base	High
0	0.24	0.3	0.36
1	0.16	0.2	0.24
2	0.08	0.1	0.12
3	0.08	0.1	0.12
4	0.04	0.05	0.06
5	0.016	0.02	0.024
6	0.008	0.01	0.012
7	0.008	0.01	0.012
8	0.004	0.005	0.006
9	0.004	0.005	0.006
10	0.004	0.005	0.006
11 - 75	0	0	0
76	0	0	0
	0.644	**0.805**	**0.966**

TABLE H.2 ASA AND CIT : PROBABILITY OF DEATH WITH SCREEN

Cycle	Low	Base	High
0	0.16	0.2	0.24
1	0.08	0.1	0.12
2	0.08	0.1	0.12
3	0.08	0.1	0.12
4	0.04	0.05	0.06
5	0.016	0.02	0.024
6	0.008	0.01	0.012
7	0.008	0.01	0.012
8	0.004	0.005	0.006
9	0.004	0.005	0.006
10	0.004	0.005	0.006
11 - 75	0	0	0
76	0	0	0
	0.484	**0.605**	**0.726**

TABLE H.3 ASA AND CIT: PROBABILITY OF MENTAL RETARDATION WITH NO SCREEN

Cycle	Low	Base	High
0	0.032	0.04	0.048
1	0.032	0.04	0.048
2	0.032	0.04	0.048
3	0.032	0.04	0.048
4	0.032	0.04	0.048
5 – 75	0	0	0
76	0	0	0
	0.16	**0.2**	**0.24**

TABLE H.4 ASA AND CIT: PROBABILITY OF MENTAL RETARDATION WITH SCREEN

Cycle	Low	Base	High
0	0.032	0.04	0.048
1	0.032	0.04	0.048
2	0.032	0.04	0.048
3	0.032	0.04	0.048
4	0.032	0.04	0.048
5-75	0	0	0
76	0	0	0
	0.16	**0.2**	**0.24**

TABLE H.5 HCY: PROBABILITY OF DEATH WITH NO SCREENING

Cycle	Low	Base	High
0	0.009	0.03	0.051
1	0.009	0.03	0.051
2	0.006	0.02	0.034
3	0.006	0.02	0.034
4	0.003	0.01	0.017
5	0.0021	0.007	0.0119
6	0.0021	0.007	0.0119
7	0.0015	0.005	0.0085
8	0.0015	0.005	0.0085
9	0.0015	0.005	0.0085
10	0.00003	0.0001	0.00017
11	0.00003	0.0001	0.00017
12	0.00003	0.0001	0.00017
13	0.00003	0.0001	0.00017
14	0.00003	0.0001	0.00017
15	0.00003	0.0001	0.00017
16	0.00003	0.0001	0.00017
17	0.00003	0.0001	0.00017
18	0.00003	0.0001	0.00017
19 -75	0	0	0
76	0	0	0
	0.04197	**0.1399**	**0.23783**

TABLE H.6 HCY: PROBABILITY OF DEATH WITH SCREENING

Cycle	Low	Base	High
0	0	0.02	0.034
1	0	0.02	0.034
2	0	0.01	0.027
3	0	0.01	0.027
4	0	0.01	0.027
5	0	0.007	0.0119
6	0	0.007	0.0119
7	0	0.005	0.0085
8	0	0.005	0.0085
9	0	0.005	0.0085
10	0	0.0001	0.00017
11	0	0.0001	0.00017
12	0	0.0001	0.00017
13	0	0.0001	0.00017
14	0	0.0001	0.00017
15	0	0.0001	0.00017
16	0	0.0001	0.00017
17	0	0.0001	0.00017
18	0	0.0001	0.00017
19-75	0	0	0
76	0	0	0
	0	**0.0999**	**0.19983**

TABLE H.7 HCY: PROBABILITY OF MENTAL RETARDATION WITH NO SCREENING

Cycle	Low	Base	High
0	0.32	0.36	0.4
1	0.2	0.225	0.25
2	0.08	0.09	0.1
3	0.04	0.045	0.05
4	0.032	0.036	0.04
5	0.0064	0.0072	0.008
6	0.0064	0.0072	0.008
7	0.0064	0.0072	0.008
8	0.0064	0.0072	0.008
9	0.0064	0.0072	0.008
10	0.0064	0.0072	0.008
11	0.0064	0.0072	0.008
12	0.0064	0.0072	0.008
13	0.0064	0.0072	0.008
14	0.0064	0.0072	0.008
15 - 75	0.000918	0.001033	0.001148
76	0.000918	0.001033	0.001148
	0.792941	**0.892058**	**0.991176**

TABLE H.8 HCY: PROBABILITY OF MENTAL RETARDATION WITH SCREENING

Cycle	low	base	high
0	0	0.04	0.09
1	0	0.02	0.04
2	0	0.01	0.02
3	0	0.01	0.02
4	0	0.005	0.001
5	0	0.001	0.002
6	0	0.001	0.002
7	0	0.001	0.002
8	0	0.001	0.002
9	0	0.001	0.002
10 - 75	0	0	0
76	0	0	0
	0	**0.09**	**0.181**

TABLE H.9 HCY: PROBABILITY OF LENS DISLOCATION WITH NO SCREENING

Cycle	Low	Base	High
0	0.005714	0.007143	0.008572
1	0.005714	0.007143	0.008572
2	0.005714	0.007143	0.008572
3	0.005714	0.007143	0.008572
4	0.005714	0.007143	0.008572
5	0.005714	0.007143	0.008572
6	0.005714	0.007143	0.008572
7	0.04	0.05	0.06
8	0.056	0.07	0.084
9	0.16	0.2	0.24
10	0.08	0.1	0.12
11	0.064	0.08	0.096
12	0.04	0.05	0.06
13	0.024	0.03	0.036
14	0.016	0.02	0.024
15 - 75	0.00264	0.0033	0.00396
76	0.00016	0.0002	0.00024
	0.567121	**0.708901**	**0.850681**

TABLE H.10 HCY: PROBABILITY OF LENS DISLOCATION WITH SCREENING

Cycle	low	base	high
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0.005	0.01
9	0	0.01	0.02
10	0	0.02	0.04
11	0	0.01	0.02
12	0	0.005	0.01
13 - 75	0	0	0
76	0	0	0
	0	**0.05**	**0.1**

TABLE H.11 HCY: PROBABILITY OF SPINAL OSTEOPOROSIS WITH NO SCREENING

Cycle	low	base	high
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0.0007	0.001	0.0013
7	0.0007	0.001	0.0013
8	0.0007	0.001	0.0013
9	0.0007	0.001	0.0013
10	0.0007	0.001	0.0013
11	0.0035	0.005	0.0065
12	0.0035	0.005	0.0065
13	0.035	0.05	0.065
14	0.035	0.05	0.065
15	0.12	0.18	0.24
16	0.035	0.05	0.065
17	0.035	0.05	0.065
18	0.021	0.03	0.039
19	0.014	0.02	0.026
20	0.007	0.01	0.013
21	0.0035	0.005	0.0065
22	0.0035	0.005	0.0065
23	0.0035	0.005	0.0065
24	0.0035	0.005	0.0065
25	0.0035	0.005	0.0065
26	0.0035	0.005	0.0065
27	0.0035	0.005	0.0065
28	0.0035	0.005	0.0065
29	0.0035	0.005	0.0065
30 - 75	0.00014	0.0002	0.00026
76	0.00014	0.0002	0.00026
	0.35058	**0.5094**	**0.66822**

TABLE H.12 HCY: PROBABILITY OF SPINAL OSTEOPOROSIS WITH SCREENING

Cycle	low	base	high
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0.005	0.01
14	0	0.01	0.02
15	0	0.02	0.04
16	0	0.01	0.02
17	0	0.005	0.01
18 - 75	0	0	0
76	0	0	0
	0	**0.05**	**0.1**

TABLE H.13 MSUD: PROBABILITY OF DEATH WITH NO SCREEN

Cycle	low	estimate	high
0	0.68	0.75	0.82
1	0.12	0.15	0.18
2 - 75	0	0	0
76	0	0	0
	0.8	**0.9**	**1**

TABLE H.14 MSUD: PROBABILITY OF DEATH WITH SCREEN

Cycle	low	estimate	high
0	0.0075	0.01	0.0125
1	0.0075	0.01	0.0125
2	0.0075	0.01	0.0125
3	0.0075	0.01	0.0125
4	0.0075	0.01	0.0125
5	0.00075	0.001	0.00125
6	0.00075	0.001	0.00125
7	0.00075	0.001	0.00125
8	0.00075	0.001	0.00125
9	0.00075	0.001	0.00125
10	0.00075	0.001	0.00125
11	0.00075	0.001	0.00125
12	0.00075	0.001	0.00125
13	0.00075	0.001	0.00125
15	0.00075	0.001	0.00125
17 - 75	0	0	0
76	0	0	0
	0.045	**0.06**	**0.075**

TABLE H.15 MSUD: PROBABILITY OF NEUROLOGICAL DAMAGE WITH NO SCREEN

Cycle	Value 1	Value 2	Value 3
0	0.015	0.02	0.025
1	0.015	0.02	0.025
2	0.015	0.02	0.025
3	0.015	0.02	0.025
4	0.0075	0.01	0.0125
5	0.00075	0.001	0.00125
6	0.00075	0.001	0.00125
7	0.00075	0.001	0.00125
8	0.00075	0.001	0.00125
9	0.00075	0.001	0.00125
10	0.00075	0.001	0.00125
11	0.00075	0.001	0.00125
12	0.00075	0.001	0.00125
13	0.00075	0.001	0.00125
15	0.00075	0.001	0.00125
17 - 75	0	0	0
76	0	0	0
	0.075	**0.1**	**0.125**

TABLE H.16 MSUD: PROBABILITY OF NEUROLOGICAL DAMAGE WITH SCREEN

Cycle	low	estimate	high
0	0.015	0.02	0.025
1	0.015	0.02	0.025
2	0.015	0.02	0.025
3	0.015	0.02	0.025
4	0.0075	0.01	0.0125
5	0.00075	0.001	0.00125
6	0.00075	0.001	0.00125
7	0.00075	0.001	0.00125
8	0.00075	0.001	0.00125
9	0.00075	0.001	0.00125
10	0.00075	0.001	0.00125
11	0.00075	0.001	0.00125
12	0.00075	0.001	0.00125
13	0.00075	0.001	0.00125
15	0.00075	0.001	0.00125
17 - 75	0	0	0
76	0	0	0
	0.075	**0.1**	**0.125**

TABLE H.17 MSUD: PROBABILITY OF DEVELOPMENTAL DELAY WITH NO SCREEN

Cycle	low	estimate	high
0	0.0075	0.01	0.0125
1	0.0075	0.01	0.0125
2	0.0075	0.01	0.0125
3	0.0075	0.01	0.0125
4	0.0075	0.01	0.0125
5	0.00075	0.001	0.00125
6	0.00075	0.001	0.00125
7	0.00075	0.001	0.00125
8	0.00075	0.001	0.00125
9	0.00075	0.001	0.00125
10	0.00075	0.001	0.00125
11	0.00075	0.001	0.00125
12	0.00075	0.001	0.00125
13	0.00075	0.001	0.00125
15	0.00075	0.001	0.00125
17 - 75	0	0	0
76	0	0	0
	0.045	**0.06**	**0.075**

TABLE H.18 MSUD: PROBABILITY OF DEVELOPMENTAL DELAY WITH SCREEN

Cycle	low	estimate	high
0	0.009	0.01	0.011
1	0.00375	0.005	0.00625
2	0.00075	0.001	0.00125
3	0.00075	0.001	0.00125
4	0.00075	0.001	0.00125
5	0.00075	0.001	0.00125
6	0.00075	0.001	0.00125
7	0.00075	0.001	0.00125
8	0.00075	0.001	0.00125
9 - 75	0	0	0
76	0	0	0
	0.018	**0.022**	**0.026**

TABLE H.19 TYROSINEMIA: PROBABILITY OF CLINICAL DIAGNOSIS WITH NO SCREEN

Cycle	Low	base	High
0	0.25	0.35	0.45
1	0.15	0.25	0.35
2	0.1	0.2	0.05
3	0.1	0.1	0.05
4	0.1	0.05	0.05
5	0.1	0.02	0.05
6	0.1	0.01	0
7	0.1	0.01	0
8	0	0.01	0
9 - 75	0	0	0
76	0	0	0
	1	**1**	**1**

TABLE H.20 TYROSINEMIA: PROBABILITY OF LIVER DAMAGE WITH NO SCREEN

Cycle	Low	Base	High
0	0.05	0.06	0.07
1	0.03	0.04	0.05
2	0.01	0.02	0.03
3 - 15	0	0	0
76	0	0	0
	0.09	**0.12**	**0.15**

TABLE H.21 MCADD: PROBABILITY OF DEATH WITH NO SCREEN

Cycle	low	base	high
0	0.108	0.12	0.132
1	0.036	0.04	0.044
2	0.009	0.01	0.011
3	0.009	0.01	0.011
4	0.009	0.01	0.011
5	0.009	0.01	0.011
6	0.009	0.01	0.011
7	0.009	0.01	0.011
8	0.009	0.01	0.011
9	0.009	0.01	0.011
10	0.009	0.01	0.011
11 - 75	0	0	0
76	0	0	0
	0.225	**0.25**	**0.275**

TABLE H.22 MCADDD: PROBABILITY OF DEATH WITH SCREEN

Cycle	low	base	high
0	0.009	0.01	0.011
1	0.009	0.01	0.011
2	0.009	0.01	0.011
3	0.0045	0.005	0.0055
4	0.0009	0.001	0.0011
5	0.0009	0.001	0.0011
6	0.0009	0.001	0.0011
7	0.0009	0.001	0.0011
8	0.00009	0.0001	0.00011
9	0.00009	0.0001	0.00011
10	0.00009	0.0001	0.00011
11	0.00009	0.0001	0.00011
12	0.00009	0.0001	0.00011
13	0.00009	0.0001	0.00011
14	0.00009	0.0001	0.00011
15	0.00009	0.0001	0.00011
16	0.00009	0.0001	0.00011
17	0.00009	0.0001	0.00011
18	0.00009	0.0001	0.00011
19	0.00009	0.0001	0.00011
20	0.00009	0.0001	0.00011
21	0.00009	0.0001	0.00011
22	0.00009	0.0001	0.00011
23	0.00009	0.0001	0.00011
24	0.00009	0.0001	0.00011
25	0.00009	0.0001	0.00011
26	0.00009	0.0001	0.00011
27	0.00009	0.0001	0.00011
28	0.00009	0.0001	0.00011
29	0.00009	0.0001	0.00011
30	0.00009	0.0001	0.00011
31	0.00009	0.0001	0.00011
32	0.00009	0.0001	0.00011
33 - 75	0	0	0
76	0	0	0
	0.03735	**0.0415**	**0.04565**

TABLE H.23 GA I: PROBABILITY OF DEATH WITH NO SCREEN

Cycle	Low	Estimate	High
0	0.018	0.02	0.022
1	0.018	0.02	0.022
2	0.018	0.02	0.022
3	0.018	0.02	0.022
4	0.018	0.02	0.022
5	0.018	0.02	0.022
6	0.018	0.02	0.022
7	0.018	0.02	0.022
8	0.018	0.02	0.022
9	0.018	0.02	0.022
10	0.018	0.02	0.022
11	0.018	0.02	0.022
12	0.018	0.02	0.022
13	0.018	0.02	0.022
14	0.018	0.02	0.022
15	0.018	0.02	0.022
16 - 75	0	0	0
76	0	0	0
	0.288	**0.32**	**0.352**

TABLE H.24 GA I: PROBABILITY OF DEATH WITH SCREEN

Cycle	Low	Estimate	High
0	0.009	0.01	0.011
1	0.009	0.01	0.011
2	0.009	0.01	0.011
3	0.009	0.01	0.011
4	0.00225	0.0025	0.00275
5	0.00225	0.0025	0.00275
6	0.00225	0.0025	0.00275
7	0.00225	0.0025	0.00275
8	0.00009	0.0001	0.00011
9	0.00009	0.0001	0.00011
10	0.00009	0.0001	0.00011
11	0.00009	0.0001	0.00011
12	0.00009	0.0001	0.00011
13	0.00009	0.0001	0.00011
14	0.00009	0.0001	0.00011
15	0.00009	0.0001	0.00011
16 - 75	0	0	0
76	0	0	0
	0.04572	**0.0508**	**0.05588**

TABLE H.25 GA I: PROBABILITY OF NEUROLOGICAL DAMAGE WITH NO SCREEN

Cycle	low	estimate	high
0	0.27	0.35	0.385
1	0.198	0.27	0.297
2	0.108	0.12	0.132
3	0.054	0.06	0.066
4	0.036	0.04	0.044
5	0.027	0.03	0.033
6	0.009	0.01	0.011
7	0.009	0.01	0.011
8	0.0045	0.005	0.0055
9	0.0045	0.005	0.0055
10	0.0045	0.005	0.0055
11	0.00009	0.0001	0.00011
12	0.00009	0.0001	0.00011
13	0.00009	0.0001	0.00011
14	0.00009	0.0001	0.00011
15	0.00009	0.0001	0.00011
16 - 75	0	0	0
76	0	0	0
	0.72495	**0.9055**	**0.99605**

TABLE H.26 GA I: PROBABILITY OF NEUROLOGICAL DAMAGE WITH SCREEN

Cycle	low	estimate	high
0	0.045	0.05	0.055
1	0.045	0.05	0.055
2	0.045	0.05	0.055
3	0.045	0.05	0.055
4	0.045	0.05	0.055
5	0.036	0.04	0.044
6	0.018	0.02	0.022
7	0.018	0.02	0.022
8	0.009	0.01	0.011
9	0.0045	0.005	0.0055
10	0.0045	0.005	0.0055
11	0.00009	0.0001	0.00011
12	0.00009	0.0001	0.00011
13	0.00009	0.0001	0.00011
14	0.00009	0.0001	0.00011
15	0.00009	0.0001	0.00011
16 - 75	0	0	0
76	0	0	0
	0.31545	**0.3505**	**0.38555**

TABLE H.27 COAD: PROBABILITY OF DEATH WITH NO SCREEN

Cycle	Low	Estimate	High
0	0.18	0.2	0.22
1	0.18	0.2	0.22
2	0.045	0.05	0.055
3	0.009	0.01	0.011
4	0.009	0.01	0.011
5	0.009	0.01	0.011
6	0.009	0.01	0.011
7	0.0045	0.005	0.0055
8	0.0045	0.005	0.0055
9	0.0045	0.005	0.0055
10 - 75	0	0	0
76	0	0	0
	0.4545	**0.505**	**0.5555**

TABLE H.28 COAD: PROBABILITY OF DEATH WITH SCREEN

Cycle	Low	Estimate	High
0	0.036	0.04	0.044
1	0.018	0.02	0.022
2	0.009	0.01	0.011
3	0.009	0.01	0.011
4	0.0045	0.005	0.0055
5	0.0045	0.005	0.0055
6	0.0045	0.005	0.0055
7	0.0045	0.005	0.0055
8	0.0045	0.005	0.0055
9	0.0045	0.005	0.0055
10 - 75	0	0	0
76	0	0	0
	0.099	**0.11**	**0.121**

TABLE H.29 COAD: PROBABILITY OF NEUROLOGICAL DAMAGE WITH NO SCREEN

Cycle	Low	Estimate	High
0	0.0081	0.009	0.0099
1	0.0081	0.009	0.0099
2	0.0405	0.045	0.0495
3	0.0405	0.045	0.0495
4	0.0405	0.045	0.0495
5	0.0405	0.045	0.0495
6	0.0405	0.045	0.0495
7	0.0405	0.045	0.0495
8	0.0405	0.045	0.0495
9	0.0405	0.045	0.0495
10	0.0639	0.071	0.0781
11	0.0639	0.071	0.0781
12	0.0639	0.071	0.0781
13	0.0639	0.071	0.0781
14	0.0639	0.071	0.0781
15 - 75	0	0	0
76	0	0	0
	0.6597	**0.733**	**0.8063**

TABLE H.30 COAD: PROBABILITY OF NEUROLOGICAL DAMAGE WITH SCREEN

Cycle	Low	Estimate	High
0	0.0054	0.006	0.0066
1	0.0054	0.006	0.0066
2	0.0108	0.012	0.0132
3	0.0108	0.012	0.0132
4	0.0108	0.012	0.0132
5	0.0135	0.015	0.0165
6	0.0135	0.015	0.0165
7	0.0135	0.015	0.0165
8	0.0135	0.015	0.0165
9	0.0135	0.015	0.0165
10	0.027	0.03	0.033
11	0.027	0.03	0.033
12	0.027	0.03	0.033
13	0.027	0.03	0.033
14	0.027	0.03	0.033
15 - 75	0	0	0
76	0	0	0
	0.2457	**0.273**	**0.3003**

TABLE H.31 COAD: PROBABILITY OF CHRONIC RENAL FAILURE WITH NO SCREEN

Cycle	Low	Estimate	High
0	0.0009	0.001	0.0011
1	0.0009	0.001	0.0011
2	0.0009	0.001	0.0011
3	0.0009	0.001	0.0011
4	0.0018	0.002	0.0022
5	0.0018	0.002	0.0022
6	0.054	0.06	0.066
7	0.054	0.06	0.066
8	0.054	0.06	0.066
9	0.054	0.06	0.066
10	0.054	0.06	0.066
11	0.045	0.05	0.055
12	0.045	0.05	0.055
13	0.0018	0.002	0.0022
14	0.0018	0.002	0.0022
15 - 75	0	0	0
76	0	0	0
	0.3708	**0.412**	**0.4532**

TABLE H.32 COAD: PROBABILITY OF CHRONIC RENAL FAILURE WITH SCREEN

Cycle	Low	Estimate	High
0	0	0	0
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0.009	0.01	0.011
7	0.009	0.01	0.011
8	0.009	0.01	0.011
9	0.009	0.01	0.011
10	0.009	0.01	0.011
11 - 75	0	0	0
76	0	0	0
	0.045	**0.05**	**0.055**

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